“ACANTHOSIS NIGRICANS – A CLINICOEPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY”

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Partial fulfilment of the University regulations for

MD DEGREE IN

DERMATOLOGY, VENEREOLOGY AND LEPROSY

(BRANCH XX)

MADRAS MEDICAL COLLEGE

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

Certified that this dissertation titled **"ACANTHOSIS NIGRICANS – A CLINICOEPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY"** is a bonafide work done by **Dr.E.BALASUBRAMANIAN** Postgraduate student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 3 during the academic year 2013 – 2016. This work has not previously formed the basis for award of any degree.

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This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai towards partial fulfillment of the rules and regulations for the award of M.D Degree in Dermatology, Venereology and Leprosy (BRANCH – XX)

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DECLARATION

I **Dr.E.BALASUBRAMANIAN** solemnly declare that the dissertation on **"ACANTHOSIS NIGRICANS – A CLINICO-EPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY "** was done by me at Madras Medical College during 2013-2016 under the guidance and supervision of Prof.**Dr.K.MANOHARAN, MD.DD.,** The HOD and professor, Department of Dermatology, Madras Medical College/RGGGH, Chennai –3.

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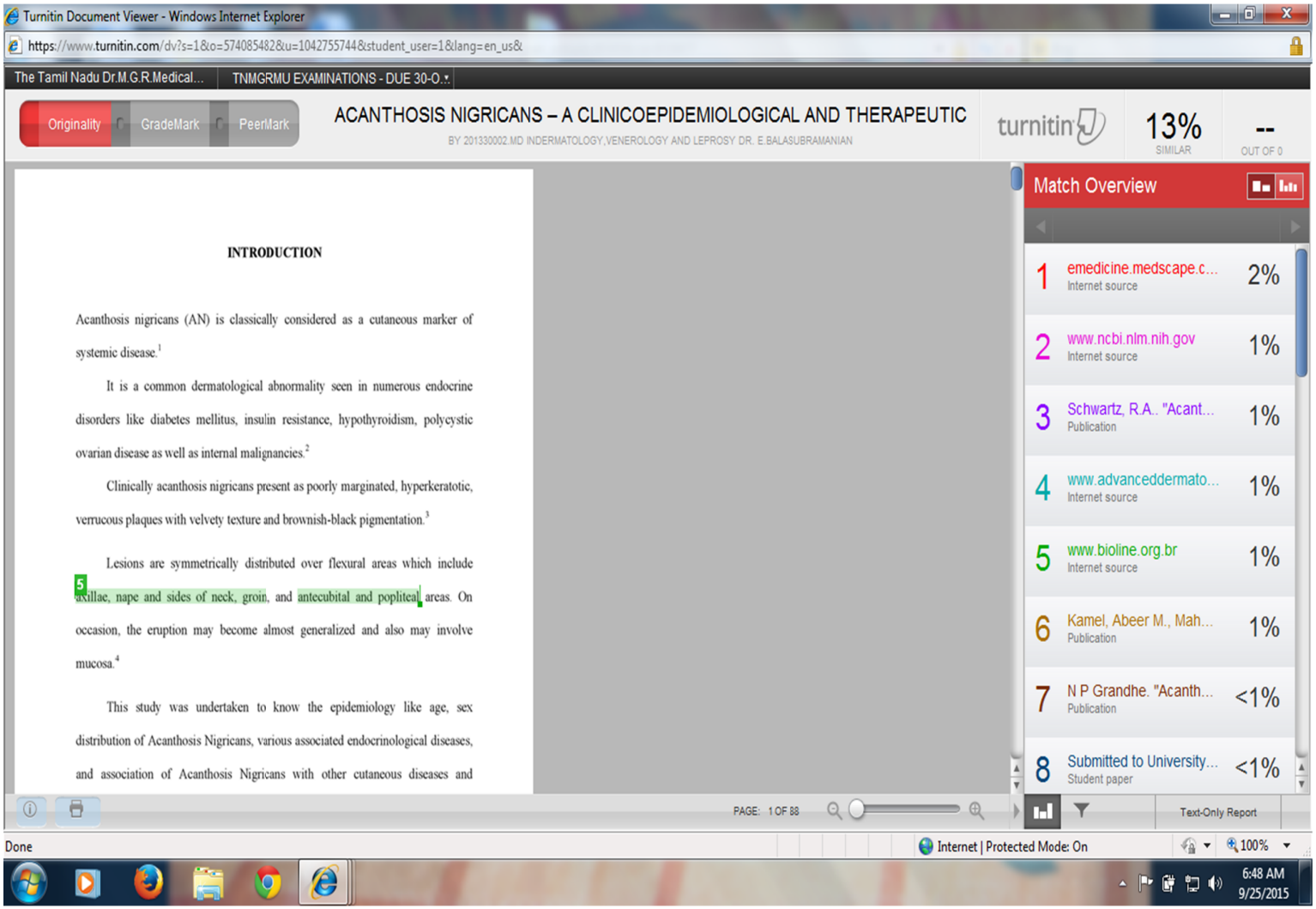
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INTRODUCTION
Acanthosis nigricans (AN) is classically considered as a cutaneous marker of systemic disease.[1]
It is a common dermatological abnormality seen in numerous endocrine disorders like diabetes mellitus, insulin resistance, hypothyroidism, polycystic ovarian disease as well as internal malignancies.[2]
Clinically acanthosis nigricans present as poorly marginated, hyperkeratotic, verrucous plaques with velvety texture and brownish-black pigmentation.[3]
Lesions are symmetrically distributed over flexural areas which include axillae, nape and sides of neck, groin, and antecubital and popliteal areas. On occasion, the eruption may become almost generalized and also may involve mucosa.[4]
This study was undertaken to know the epidemiology like age, sex distribution of Acanthosis Nigricans, various associated endocrinological diseases, and association of Acanthosis Nigricans with other cutaneous diseases and
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ACANTHOSIS NIGRICANS – A CLINICOEPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY

ABSTRACT

INTRODUCTION

Acanthosis nigricans is characterized by velvety, brownish black pigmentation of flexural areas. Acanthosis nigricans is considered as a marker of internal diseases like insulin resistance, diabetes, hypothyroidism, polycystic ovarian disease and rarely internal malignancies.

AIMS AND OBJECTIVES

The study aims to

1) Study the epidemiology of Acanthosis Nigricans
2) Find out associated common endocrinological diseases
3) Compare the effectiveness of various topical therapeutic modalities

MATERIALS AND METHODS

Hundred patients of acanthosis nigricans were selected. Relevant investigations like blood sugar, fasting lipid profile, thyroid profile and ultrasound abdomen were done. Body mass index was calculated for all patients. Patients were then randomly divided into 5 treatment groups of 20 patients each. Group A receiving Topical 0.05% tretinoin, Group B receiving topical 0.005% calcipotriol,

Group C receiving topical triple combination cream containing Hydroquinone 2%, tretinoin 0.05% and Fluocinolone acetonide 0.01%, Group D treated with 35% Trichloroacetic acid peel and Group E treated with 50% Glycolic acid peel.

OBSERVATION AND RESULTS

Acanthosis nigricans was more common in females than males with a ratio of 2.22: 1 and the mean age was 22.24 years. Nearly seventy percent of patients had abnormal body mass index. Acrochordon was the most common associated dermatological finding. Diabetes was the most common endocrine abnormality present in 41% of patients followed by dyslipidemia and hypothyroidism. Nearly 19% of the female patients had polycystic ovarian disease. Chemical peeling with trichloro acetic acid had the maximum response percentage of 75% and topical calcipotriol had the least response percentage of 25%.

CONCLUSION

In our study age, sex and site distribution were in concurrence with the previous studies. Topical treatment need to be given for longer period with simultaneous treatment of endocrine disorders and obesity for better results.

KEY WORDS

Acanthosis nigricans, insulin resistance and poly cystic ovarian disease.

INTRODUCTION

Acanthosis nigricans (AN) is classically considered as a cutaneous marker of systemic disease.[1]

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This study was undertaken to know the epidemiology like age, sex distribution of Acanthosis Nigricans, various associated endocrinological diseases, and association of Acanthosis Nigricans with other cutaneous diseases and effectiveness of various topical treatments.

Review of Literature

REVIEW OF LITERATURE

Acanthosis nigricans was coined by Unna which literally means black thorn. The Word acanthosis was derived from Greek meaning thorn and nigricans from Latin meaning black.[5]

Pollitzer, Unna's student reported the first case in 1890. In the same year, Janovsky also described the first case.[6]

Curth clinically classified Acanthosis Nigricans as benign, malignant, syndromic and pseudo-acanthosis nigricans.[7]

Schwartz in 1994 classified Acanthosis Nigricans into eight types [8]

1. Acral
2. Benign
3. Malignant
4. Medication induced
5. Obesity associated
6. Syndromic
7. Unilateral
8. Mixed type

PREVALENCE

The prevalence in general population is not known. Prevalence of Acanthosis Nigricans has been increasing recently due to the rising prevalence of obesity and Diabetes observed recently. It ranges from 7% to 74%, according to age, race, degree of obesity and concomitant endocrinopathy. Hud *et al*. demonstrated that prevalence among black women was higher compared to white women.[9]

In India only few studies with prevalence in certain subpopulations are available. In a study conducted at Kerala in 2008, 16.1 % of 3069 adults aged more than 18 years were found to have acanthosis nigricans. Prevalence among females was significantly higher (19.6%) than males (11.4%) and it was highest in 30-40 year age group. Obesity, high triglyceride levels and presence of diabetes correlated positively with prevalence of Acanthosis Nigricans.[10]

In a study conducted at tertiary referral hospital in north India in 2004 among 150 diabetics and 150 non diabetic matched controls the prevalence of Acanthosis Nigricans was 62.6% and 40% in subjects with diabetes and healthy controls respectively. The severity of Acanthosis Nigricans was found to increase with increasing BMI, waist-hip ratio, skinfold thickness, and body fat percentage in diabetic patients.[11]

SIGNIFICANCE

Obesity and insulin resistance are linked to most cases of Acanthosis Nigricans. In diabetes Acanthosis nigricans is probably the most readily recognized skin manifestation.[12]

Acanthosis Nigricans may be considered as a predictor for type 2 diabetes years before onset of other symptoms of diabetes mellitus.[13]

Clustering of several risk factors constitutes metabolic syndrome which includes central obesity, glucose intolerance, hyperinsulinemia, low HDL cholesterol, high triglycerides and hypertension. Metabolic syndrome is associated with five-fold greater risk of developing type 2 diabetes and is also a risk factor for mortality due to cardiovascular disease. Acanthosis nigricans has high specificity and good sensitivity as a marker for metabolic syndrome.[14]

AETIOPATHOGENESIS

The central role in pathogenesis of Acanthosis nigricans is played by Insulin.

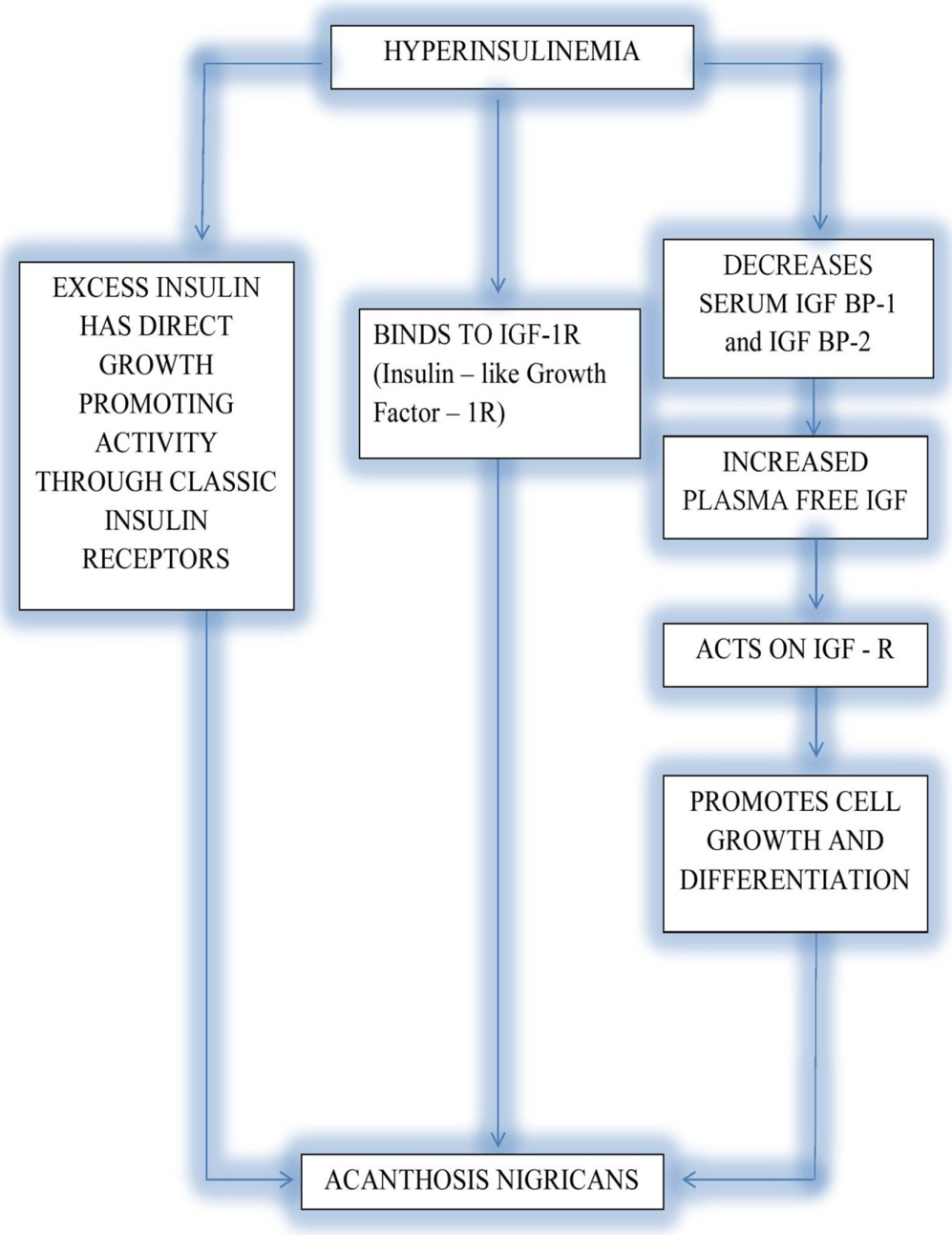
Genetic predisposition

Benign acanthosis nigricans and unilateral or nevoid acanthosis nigricans follows an autosomal dominant inheritance with variable penetrance.

Hyperinsulinemia

Insulin in addition to its metabolic effects has growth promoting action also. At low concentrations insulin binds to insulin receptors which have metabolic activity and weak growth promotion activity. At high concentrations insulin binds to IGF-1 R (insulin like growth factor receptor -1) which has more potent growth promoting effect. IGF-1 receptors are expressed in basal keratinocytes and fibroblasts and excess insulin acting through these receptors causes epidermal and fibroblast proliferation leading to acanthosis nigricans. [12, 15]

Normally IGF is bound to IGF binding proteins (IGFBP). In obese patients with hyperinsulinemia IGFBP levels are decreased leading to increase in concentration of free Insulin like Growth Factor that leads to increased cell growth and differentiation.[15, 16]


HYPERINSULINEMIA
EXCESS INSULIN HAS DIRECT GROWTH PROMOTING ACTIVITY THROUGH CLASSIC INSULIN RECEPTORS
BINDS TO IGF-1R (Insulin – like Growth Factor – 1R)
DECREASES SERUM IGF BP-1 and IGF BP-2
INCREASED PLASMA FREE IGF
ACTS ON IGF - R
PROMOTES CELL GROWTH AND DIFFERENTIATION
ACANTHOSIS NIGRICANS

CLINICAL FEATURES

Clinical morphology is the same for various types though it may vary in severity and distribution. Acanthosis Nigricans usually begins as grey brown or black pigmentation with dryness and roughness of the skin which later becomes palpably thickened. Later small papillomatous elevations arise from thickened skin giving rise to velvety texture. With further thickening skin markings become accentuated and surface becomes mammilated or rugose. Often asymptomatic, it may be occasionally pruritic. Mostly symmetrically distributed affecting commonly back and sides of neck, axillae, groin, and antecubital and popliteal areas in the order of decreasing frequency.[15]

Neck is the most common area affected. In children with acanthosis nigricans neck involvement is seen in 99% of children compared to axilla 73%. [17]

In cases of malignancy associated acanthosis nigricans skin lesions may be generalized and mucosal involvement may be there.[52]

Burke et al proposed grading of acanthosis nigricans severity at neck. [18]

- Grade 0 – not visible on close inspection
- Grade 1 – clearly visible on inspection but with indistinct extent
- Grade 2 – lesions only at base of skull not extending to lateral margins
- Grade 3 – lesions extending to sides of neck but not visible on front of neck
- Grade 4 – lesions extending to front of neck

Neck texture [19]

0 - Smooth to touch: no differentiation from normal skin to palpation,

1 - Rough to touch: clearly differentiated from normal skin

2 - Coarseness can be observed visually, portions of the skin clearly rose above other areas

3 - Extremely coarse: “hills and valleys” observable on visual examination

Insulin resistance (IR)

A metabolic disorder characterized by failure of target cells to respond to normal levels of circulating insulin resulting in compensatory hyperinsulinemia. It is especially found in individuals with type 2 diabetes mellitus and obesity. Insulin resistance occurs in 20 to 25% of the normal individuals.

Insulin resistance is of 3 types:

(i) Type A, characterized by reduction and dysfunction of insulin receptors

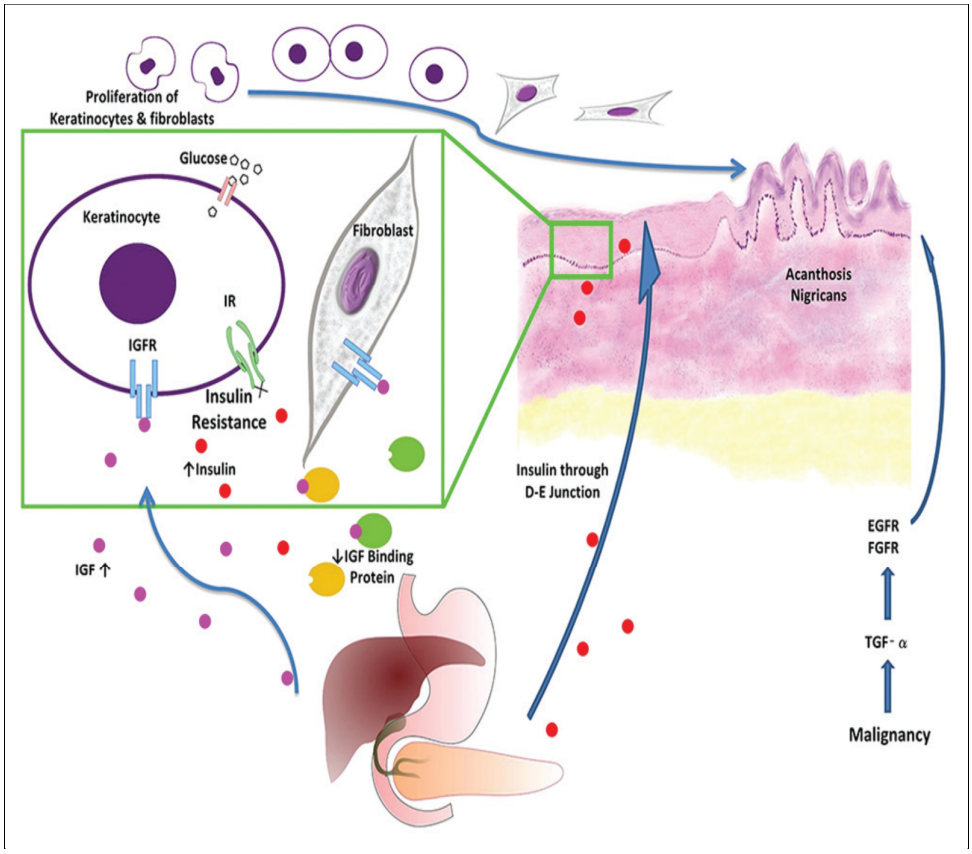
(ii) Type B, produced by antibodies against insulin receptors

(iii) Type C is a post-receptor defect.

Obese patients and patients with polycystic ovary syndrome (PCOS) have type-A insulin resistance.[20]

Higher grades of acanthosis nigricans on the neck and axilla are sensitive markers for Insulin resistance and can be used as a clinical surrogate for assessment of severity of insulin resistance. It is better marker of insulin resistance than the traditionally used markers. [21, 22]

Insulin Resistance, whatever may its cause, stimulates insulin secretion and the excess insulin level stimulates IGF-1 receptors on various tissues including skin, where stimulation of the IGF - 1 receptors on keratinocytes lead to excessive epidermal growth.[23]



HISTOPATHOLOGY [24, 25]

Histopathology of typical cutaneous Acanthosis nigricans lesions shows following characteristic findings

- Hyperkeratosis
- Papillomatosis resulting from the finger-like upward projection of dermal papillae which are covered by thinned epidermis
- 'Valleys' between these papillary projections showing mild canthosis with overlying hyperkeratosis. Acanthosis is only mild and irregular.

- Pigmentation of the lesions result primarily from the hyperkeratosis, though there is minimal hyperpigmentation of the basal layers.

Thus acanthosis nigricans is a misnomer as there is neither prominent acanthosis nor hypermelanosis in histology.

Histopathological differential diagnosis [24, 25]

1. Linear verrucous epidermal nevus
2. Seborrheic keratosis – hyperkeratotic type
3. Verruca vulgaris
4. Acrokeratosis verruciformis of Hopf
5. Acanthosis nigricans type of mycosis fungoides

All these conditions are characterized by hyperkeratosis, acanthosis and papillomatosis.

TYPES OF ACANTHOSIS NIGRICANS

Obesity-associated Acanthosis Nigricans

It is the most common type of acanthosis nigricans - once called pseudo acanthosis nigricans. It is more common in adulthood, though lesions may appear at any age. Severity of the lesion is weight dependent and with weight reduction acanthosis nigricans lesions may completely regress. Often Insulin resistance is present.[17]

Benign acanthosis nigricans

This rare genodermatosis may be present at birth or in early childhood and have a familial pattern. It is inherited as an autosomal dominant trait with variable phenotypic penetrance. It usually increases until puberty, after which it remains stationary or decreases. Obesity is not a factor.[26, 27, 8]

Benign acanthosis nigricans has predilection for axilla and often there is exacerbation at puberty. They are not reversible with weight reduction unlike obesity associated type. [26]

Syndromic Acanthosis Nigricans

Acanthosis Nigricans when associated with a syndrome is called syndromic acanthosis nigricans.

In addition to insulin resistance, acanthosis nigricans has been associated with numerous syndromes. Following 2 types are special examples

1. Type A syndrome and
2. Type B syndrome.

The type A syndrome also termed as HAIR-AN syndrome presenting with hyperandrogenemia, insulin resistance and acanthosis nigricans syndrome. Primarily affecting young women this syndrome is often familial. It is associated with polycystic ovaries or signs of virilization. The lesions of acanthosis nigricans may arise during infancy and progress rapidly during puberty.

The type B syndrome commonly occurs in women who have uncontrolled diabetes mellitus, ovarian hyperandrogenism, or an autoimmune disease such as systemic lupus erythematosus, scleroderma, Sjögrensyndrome, or Hashimoto thyroiditis. Circulating antibodies to the insulin receptor may be present. Here severity of acanthosis nigricans varies.[17, 28, 29]

Other Syndromes associated with acanthosis nigricans [8, 9]

1. Polycystic ovarian syndrome
2. Cushing syndrome
3. Down syndrome
4. Bloom syndrome
5. Costello syndrome
6. Marfan syndrome
7. Hirschowitz syndrome
8. Capozucca syndrome
9. Hermansky-Pudlack syndrome
10. Kabuki syndrome
11. Rud syndrome
12. Prader-Willi syndrome
13. Alstrom syndrome
14. Rabson-Mendenhall syndrome
15. Hypogonadal syndrome
16. Acral hypertrophy syndrome
17. Ataxia telangiectasia
18. Crouzon's syndrome

Polycystic ovary syndrome [17, 55]

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women affecting 5-10% of reproductive aged women. It is characterized by hyperinsulinemia and raised androgen levels.

Presence of significant number of the following criteria was considered in diagnosing PCOS

- History of anovulation and/or menstrual irregularities
- Hirsutism and/or temporal balding, oily skin and acne vulgaris
- Elevated serum-free testosterone and/or elevated luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio and
- Ultrasonographic finding of polycystic ovaries

The PCOS has number of dermatologic manifestations of hyperandrogenism like hirsutism, acne vulgaris and androgenetic alopecia. Acanthosis nigricans, a cutaneous sign of hyperinsulinemia may also be present. These findings provide early clinical clues to recognition of PCOS and treatment of these cutaneous conditions may improve the patient's quality of life and psychologic well-being.

Treatment modalities mainly include hormonal therapy.

Metabolic diseases with acanthosis nigricans

1. Addison's disease
2. Hypothyroidism
3. Primary biliary cirrhosis
4. Hirsutism
5. Acromegaly
6. Gigantism
7. Pseudoacromegaly
8. Lipoatrophic diabetes
9. Leprechaunism

Nevoid Acanthosis Nigricans [29]

Also known as Unilateral acanthosis nigricans, it is a rare form inherited as an irregularly autosomal dominant trait that first becomes evident at birth, in childhood, or during puberty. It is not associated with syndromes, drugs, endocrinopathies, or malignancies. After enlarging for a certain period it either remains stationary or starts regressing.

It resembles naevus unuis lateralis which is characterized by unilateral dry keratosis, presence of palmoplantar keratoderma and summer improvement.[5]

Acral Acanthosis Nigricans [8]

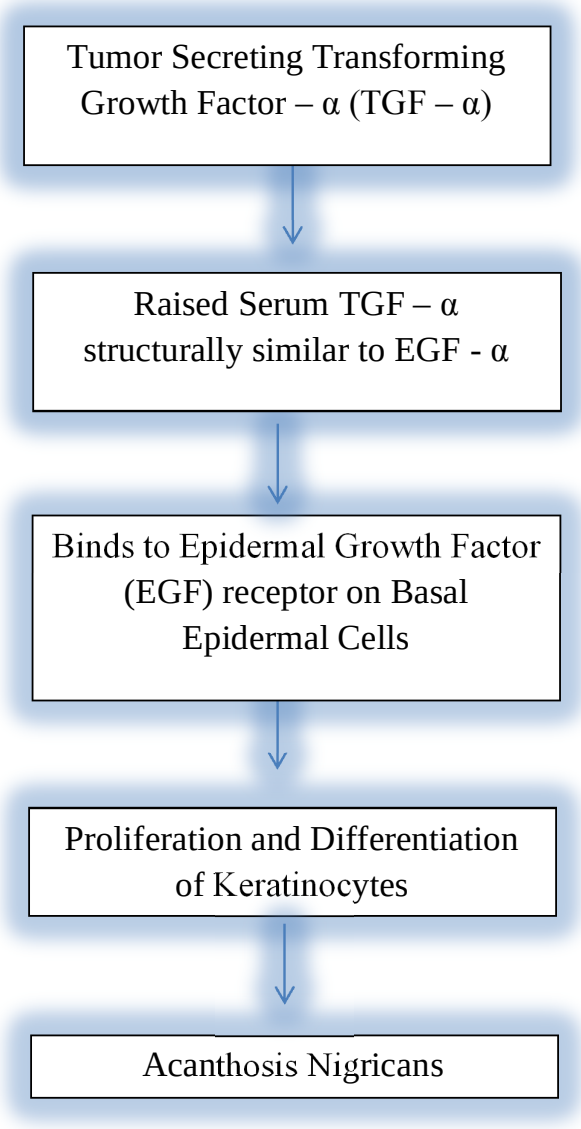
Common in dark-skinned people it is characterized by velvety hyperkeratosis of the dorsum of the hands and feet. Generally health of these persons will be good.

Malignant Acanthosis Nigricans

Acanthosis nigricans may be associated with many kinds of internal cancers, the most common being gastric adenocarcinoma. It is the most worrisome of the variants of acanthosis nigricans. It is differentiated from benign types by its sudden onset, presence of symptoms, more extensive involvement and atypical locations. Malignant acanthosis nigricans regresses with treatment of the underlying malignancy and reappears following recurrence or metastasis of the primary tumor.[30]

Malignant acanthosis nigricans is a result of tumor cell expression of peptides that enhance cellular proliferation including transforming growth factor and epidermal growth factor. These factors secreted by the tumor binds to epidermal growth factor receptors and this in turn activates the Akt intracellular signaling pathway known to be involved in keratinocyte proliferation and epidermal thickening.[31,32]

MALIGANANT ACANTHOSIS NIGRICANS



Malignant acanthosis nigricans is most commonly associated with gastrointestinal adenocarcinomas particularly gastric carcinoma. Other malignancies are those involving bronchus, bile duct, ovary, pancreas, gall bladder, endometrium, thyroid and breast.[33, 34, 35, 36]

Tripe palms:

Hyperkeratosis of the palms and soles (tylosis) along with involvement of the flexor surfaces of the fingers and toes, roughening and thickening of the fingerprints with prominence of the creases and a yellow hue may occur with malignancy associated acanthosis nigricans. This epidermal thickening may be exuberant and produce a rugose appearance with deep sulci labeled "tripe palms." Mucosal involvement tend to be more common with malignant acanthosis nigricans.[8]

Drug Induced Acanthosis Nigricans

It is a rare and reversible type of acanthosis nigricans. Certain drugs act at cell receptor level and produce acanthosis nigricans. Mechanism of occurrence of this type of acanthosis nigricans is due to induction of a temporary state of insulin resistance which in turn produces acanthosis nigricans. Subcutaneous insulin injection causes localized acanthosis nigricans.[37]

Common drugs implicated are

- Systemic corticosteroids
- Nicotinic acid
- Estrogens such as diethylstilbestrol
- Insulin
- Triazinate – folic acid antagonist
- Methyltestosterone
- Oral contraceptives
- Fusidic acid
- A melanocyte-stimulating hormone preparation composed of a crude extract of bovine pituitaries has been found to induce Acanthosis Nigricans [38, 39, 40, 41, 42]

Mixed-type Acanthosis Nigricans

When a patient with one of the above types of acanthosis nigricans develops new lesions of a different etiology, it is called Mixed-type acanthosis nigricans. Patient with obesity-associated acanthosis nigricans subsequently developing malignant acanthosis nigricans is an example.[17]

Differential diagnosis

A. Cutaneous acanthosis nigricans [8, 9]

1. Confluent and reticulated papillomatosis – Presents as skin coloured or erythematous or hyperpigmented macular lesions over intermammary and upper lateral trunk.
2. Intertriginous granular parakeratosis - Presents as erythematous to brownish hyperkeratotic papules and plaques in the intertriginous regions and is seen in middle aged women in axillae, but inguinal and submammary folds may be involved.
3. Haber syndrome - Characterized by rosacea like facial dermatoses and multiple verrucous lesions on non-sun-exposed skin.
4. Dowling - Degos disease also known as reticulate pigmented anomaly of the flexures is a familial nevoid condition presenting with progressive brown black hyperpigmentation of the flexures. There will be associated follicular hyperkeratosis.
5. Acropigmentation reticularis of Kitamura - Presents as freckle like areas of pigmentation on the dorsal aspects of hands later involving other areas of body. Palmar pits and breakage of epidermal ridge pattern are also present.
6. Nevus unuis lateralis sometimes resembles unilateral acanthosis nigricans.

7. Ichthyosis hystrix, melanocytic naevi, Becker's nevus, Pellagra, hemochromatosis, or Addison's disease are other differential diagnosis

B. Oral Mucosal acanthosis nigricans [8, 9]

Mucosal involvement occurs frequently in malignant type of Acanthosis nigricans.

Following are the differential diagnosis for mucosal acanthosis nigricans

1. Cowden's disease
2. Dyskeratosis congenita
3. Pyostamitis vegetans
4. Pachyonychia congenita
5. Wegener's Granulomatosis

TREATMENT OF ACANTHOSIS NIGRICANS

Main goal of therapy is to correct the underlying condition. There is no treatment of choice and no randomized controlled studies regarding treatment of acanthosis nigricans is available. Improvement of skin condition is patient's main concern and the treatment is mainly for cosmetic purpose only. [9, 17]

Exercise and weight reduction increases the sensitivity to insulin and reduces hyperkeratotic lesions. Removal or replacement of offending drug leads to improvement in drug induced acanthosis nigricans .[9, 17]

In cases of malignancy associated acanthosis nigricans treatment and removal of underlying malignancy leads to improvement.[32, 33]

Various topical and systemic agents are tried

TOPICAL DRUGS [2, 9]

1. Tretinoin
2. Calcipotriol
3. Triple cream containing tretinoin 0.05%, hydroquinone 4% and fluocinolone acetonide 0.01%
4. Combinations of tretinoin cream with 12% ammonium lactate cream,
5. Podophyllin, urea and salicylic acid are tried with limited success

SYSTEMIC DRUGS [2, 9, 16, 53]

1. Oral retinoids like acitretin or isotretinoin. Acitretin in an initial dose of 50mg followed by maintanence dose of 25 mg was used with some success. The mechanism of action is probably normalization of epithelial growth and differentiation

2. Metformin and rosiglitazone are useful in Acanthosis nigricans characterized by insulin resistance. Metformin and thiazolidines acts by increasing peripheral sensitivity to insulin.
3. Oral octreotide has also been used with moderate success. Octreotide is a synthetic analog of the hypothalamic hormone somatostatin. Octreotide has a higher affinity for inhibition of glucagon, growth hormone, and insulin release compared with somatostatin. Octreotide 50 μcg was used subcutaneously 3 times daily. It acts by decreasing insulin secretion.
4. Fish oil containing omega-3 fatty acids has been found to effectively reduce hyperpigmentation and normalized skin texture in a patient with acanthosis nigricans.

LASER [8,60]

Long-pulsed lasers have been tried. Recently, long-pulsed alexandrite laser was used to successfully treat acanthosis nigricans of the axilla. They act by causing photothermolysis.

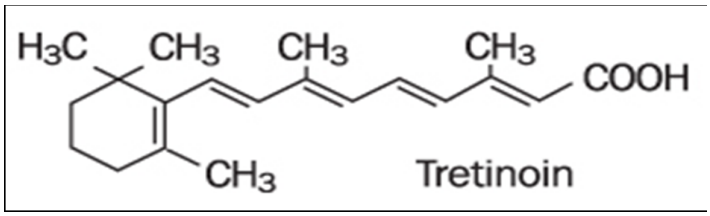
SURGICAL PROCEDURES [57]

Dermabrasion involves removal of skin layers with either manual or motorized abraders. This wound is allowed to heal by secondary

intention so that a resurfacing effect will occur. Dermabrasion has been used with success for acanthosis nigricans.

TRETINOIN [43, 44, 45, 46]

Tretinoin - all-*trans* retinol represents an oxidized form of all-*trans* retinol is a naturally occurring retinoid.



Mechanism of action

- Transcription of genes that affects growth and differentiation of cells in the skin
- Normalization of follicular epithelial differentiation and keratinization

In acanthosis nigricans it acts by producing comedolysis and also have palliative effects on fine wrinkling, mottled hyperpigmentation, and roughness of skin.

All-*trans* retinoic acid binds to cytosolic all-*trans* retinoic acid-binding protein (CRABP). CRABP II is predominant in human skin and is the determining factor in the bioavailability of retinoids. Then it is transported to the nucleus by CRABP type II, where it binds to nuclear

retinoic acid receptors (RAR) and fatty acid-binding protein 5 (FABP5) and serves as a ligand for peroxisome proliferator-activated receptor β/δ (PPAR β/δ).

Drug–RAR complexes subsequently binds to retinoic acid response elements (RARE), which are gene transcription enhancing elements leading to inhibition of cell growth. All-*trans* retinoic acid isomerizes to form 9-*cis* retinoic acid which binds to retinoid X receptors (RXR). RAR and RXR bind together as heterodimers to function as transcription factors. A number of all-*trans* retinoic acid responsive genes have been identified including

1) type I epidermal transglutaminase,
2) CRBP,
3) CRABP,
4) RAR and
5) PPAR β/δ.

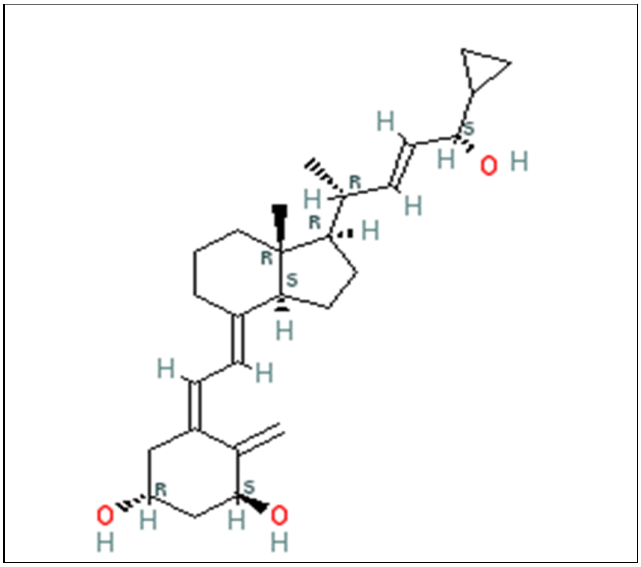
Tretinoin also reduces the release of certain inflammatory mediators, including interleukins 1β, -6, -12, TNF-α, and IFN-γ.

Irritation and erythema are the common side effects.

They are category C pregnancy drugs.

CALCIPOTRIOL [47, 48]

Calcipotriol is a synthetic vitamin D analog. In skin it acts by binding to vitamin D3 receptors present in keratinocytes, melanocytes, dermal fibroblasts and many other cell types. Drug – receptor complex in association with retinoid X receptor RXR binds to vitamin D 3 responsive elements.



It acts by inhibiting cell proliferation and induces terminal differentiation in human keratinocytes. This reduction in number of keratinocytes minimizes the effects of excess insulin. In addition it has anti-inflammatory and immune modulatory action through inhibition of IL-2 and IL-6 production by T cells. It also has inhibitory action over cytotoxic T cells and NK cells. Thus skin conditions characterized by hyperkeratosis, acanthosis and hyper proliferation like psoriasis and

acanthosis nigricans can be treated with topical calcipotriol. It is used as 0.005% cream. Side effects include erythema, hypercalcemia and irritation.

TOPICAL TRIPLE CREAM [49, 54, 55]

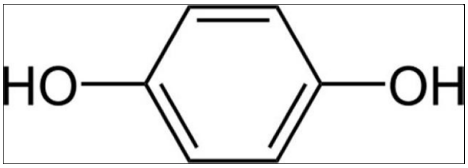
A triple combination cream containing tretinoin, 0.05%, hydroquinone 4%, and fluocinolone acetonide 0.01% was tried recently for treatment of Acanthosis nigricans.

Effectiveness depends on the following actions

1) Tretinoin 0.05%

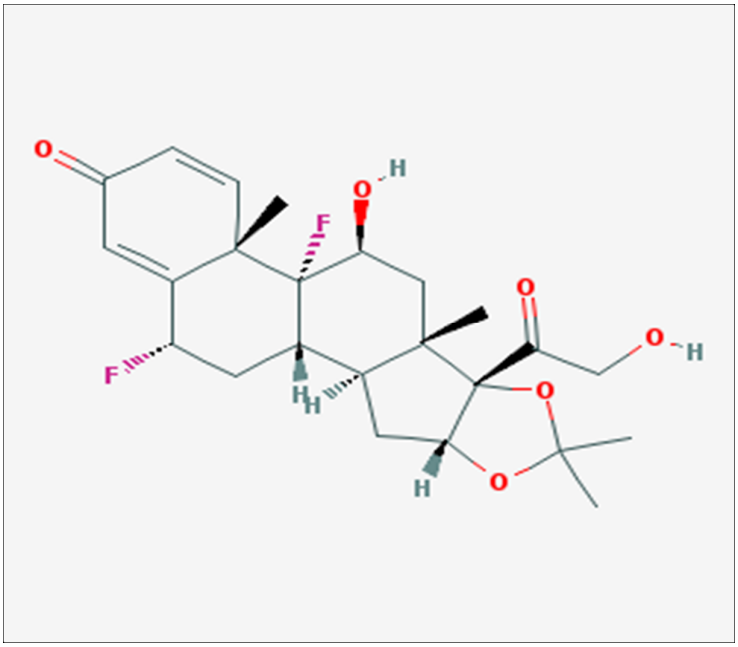
   Normalization of epidermal turn over

2) Hydroquinone 2%



Hydroquinone also known as 1, 4-dihydroxybenzene. It is an active agent that reduces melanocyte pigment production through degradation of melanin by auto-oxidation, tyrosinase inhibition, and formation of highly reactive oxygen radicals like semiquinones and quinones. These reactive substances prevent melanin production.

3) Fluocinolone acetonide 0.01% [49,54]



Fluocinolone acetonide is an high potent topical corticosteroid (TCS) that acts by many ways.

Mechanism of action

TCS elicit their effects via binding to and activating GCR as follows

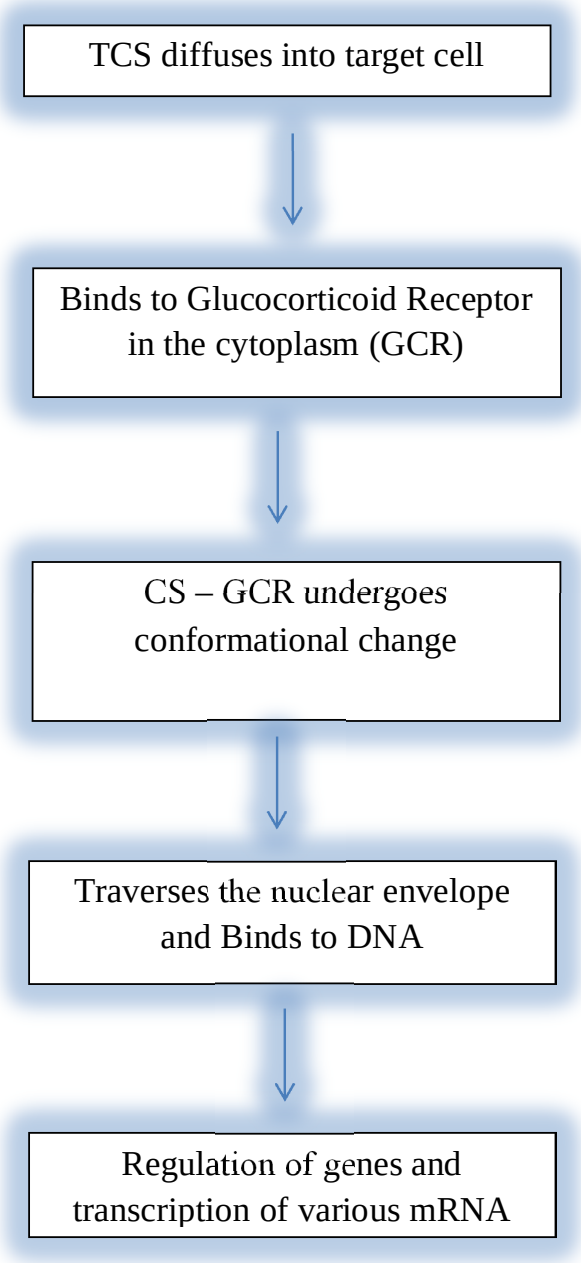
1) The corticosteroid diffuses into the target cell and binds to the GCR in the cytoplasm.
2) The corticosteroid-GCR complex undergoes necessary conformational changes.

3) The resulting active complex traverses the nuclear envelope and directly or indirectly binds to DNA.
4) Gene regulation and transcription of various specific messenger ribonucleic acid (mRNA) occur.

GCR are nearly ubiquitously expressed in human cells. TCS produce a myriad of actions. Both positive and negative gene regulation occurs. Negative gene regulation has been associated with anti-inflammatory action whereas positive gene regulation has been associated with some adverse effects.

In acanthosis nigricans , topical corticosteroid

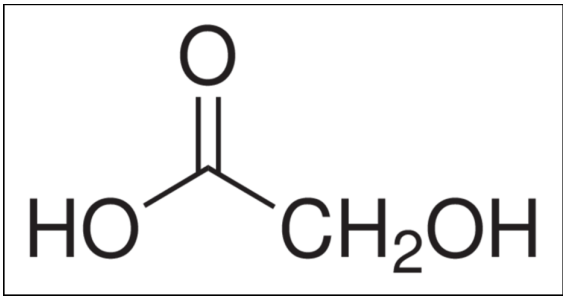
- Decreases Number of keratinocyte mitoses
- Reduces Stratum corneum thickness
- Flattens basal layer keratinocytes
- Suppression of Keratinocyte growth factors
- Inhibition of Melanocyte pigment production
- Reduces the irritation due to retinoid.


TCS diffuses into target cell
Binds to Glucocorticoid Receptor in the cytoplasm (GCR)
CS – GCR undergoes conformational change
Traverses the nuclear envelope and Binds to DNA
Regulation of genes and transcription of various mRNA

CHEMICAL PEELING [50]

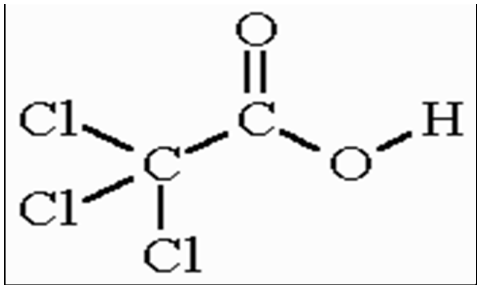
Chemical peeling agents act by causing controlled destruction of skin followed by regeneration and remodeling of skin without scarring.

Glycolic Acid [50]



Glycolic acid is an alpha hydroxic acid. It has lytic action on corneodesmosomes causing exfoliation and reduction of stratum corneum thickness. In the dermis it causes stimulation of fibroblasts and synthesis of glycosaminoglycans, collagen and elastin. A faint erythema is the end point. As they are not self-neutralizing they need to be neutralized with a solution saturated with sodium bicarbonate.

Trichloroacetic Acid [51]



Trichloroacetic acid acts by causing coagulation of proteins which is seen as frosting. It doesn't need any specific neutralizer as TCA is neutralized by serum in deep dermal vasculature. Concentration of TCA determines the depth of peel. Inflammation and activation of wound repair mechanisms follow coagulation leading to reepithelialization with replacement by smoother skin with even tone.

Aims & Objectives

AIMS AND OBJECTIVES

The study aims to

1) Study the epidemiology of Acanthosis Nigricans
2) To find out associated common endocrinological diseases
3) To compare the effectiveness of various topical therapeutic modalities

Materials and Methods

MATERIALS AND METHODS

For the present study 100 cases of Acanthosis nigricans were randomly selected from the outpatient clinic in the Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai from October 2014 to august 2015. The study was started after obtaining approval from Institutional Ethical Committee.

STUDY DESIGN - Prospective study

SUBJECT SELECTION

Inclusion Criteria

1. All patients presented with clinical features of acanthosis nigricans in dermatology outpatient department were selected.
2. All patients who were willing to participate in study.

Exclusion Criteria

1. Patients who were already treated or undergoing other modes of treatment for Acanthosis nigricans.
2. Patients who were not willing to participate in the study.

The diagnosis was based on clinical history and morphology of lesions. The selected patients were clearly explained about the natural

course of the disease, the possible benefits and side effects of treatment. Informed written consent was obtained from all the participants before initiating treatment.

All the patients are evaluated as follows

1. History

Detailed case history of each patient with reference to the duration and course of the disease, obesity, diabetes, thyroid related illness, menstrual abnormalities, family history and recent drug intake were taken.

2. General examination:

Height, weight and Body mass index were noted. Other general examination findings like anaemia, jaundice and lymphadenopathy were noted.

3. Systemic examination

Examination of cardiovascular, respiratory, gastrointestinal and central nervous system was done for all patients.

4. Dermatological Examination

Clinical features like sites of involvement, morphology of lesions, symmetry, and other associated systemic and cutaneous disorders were

noted. Initial grading of acanthosis nigricans is noted using Burke et al grading of Acanthosis nigricans severity.

5. Investigations

Following investigations were done in all patients

a. Thyroid function test
b. Fasting and post prandial blood sugar
c. Fasting lipid profile
d. Complete Blood haemogram
e. Peripheral smear
f. Liver function tests
g. Renal function tests
h. USG abdomen for all female patients to rule out PCOD.

Those patients with associated endocrinological abnormalities were treated for endocrinological abnormalities and those who are obese were advised weight reduction strategies.

For treatment of Acanthosis nigricans patients were randomly divided into five groups with 20 patients in each group.

- Group A - Topical 0.05% tretinoin
- Group B - Topical 0.005% calcipotriol.

- Group C - Topical triple combination cream containing Hydroquinone 2%, Tretinoin 0.05% and Fluocinolone acetonide 0.01%
- Group D - Chemical peeling with 35% Trichloroacetic acid
- Group E - Chemical peeling with 50% Glycolic acid

1. Group A

Twenty patients were randomly selected. After completing preliminary investigations these patients were treated with topical 0.05% tretinoin. Patients were advised to apply it daily once overnight for a period of 12 weeks.

2. Group B

Twenty patients were randomly selected. After completing preliminary investigations these patients were treated with topical 0.005% calcipotriol. Patients were advised to apply it daily once overnight for a period of 12 weeks

3. Group C

Twenty patients were randomly selected. After completing preliminary investigations these patients are treated with topical triple combination cream containing Hydroquinone 2%,

Tretinoin 0.05% and Fluocinolone acetonide 0.01%. Patients were advised to apply it daily once overnight for a period of 12 weeks

4. Group D

Twenty patients were randomly selected. After completing preliminary investigations these patients were treated with chemical peeling with 35% Trichloroacetic acid at 3 weekly intervals for a total period of 12 weeks.

5. Group E

Twenty patients were randomly selected. After completing preliminary investigations these patients were treated with chemical peeling with 50% Glycolic acid at 3 weekly intervals for a total period of 12 weeks.

All the patients are followed up at the interval of 3 weeks and at the end of 12 weeks, grading of acanthosis nigricans is again noted using Burke et al grading of Acanthosis nigricans severity.

STATISTICAL ANALYSIS:

The collected data was entered for analysis in Microsoft Excel. This data was exported to Statistical Package for Social Sciences software (SPSS) version 21. Mean, standard deviations and range were employed to describe continuous variables, while frequency distributions were obtained for dichotomous variables. Associations between qualitative variables were done using Chi square tests, Fisher's exact test. A P value of less than 0.05 has been considered to be significant.

Observations & Results

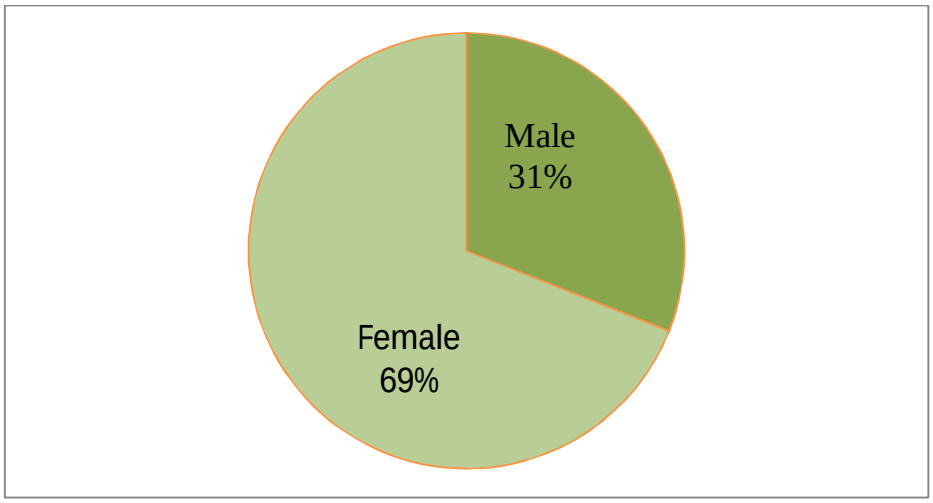
OBSERVATION AND RESULTS

Table :1 **AGE DISTRIBUTION OF OF ACANTHOSIS NIGRICANS**

SI.No	Age Group in Years	Male	Female	Total No.Of Cases
1	1 to 10	2	1	3
2	11 to 20	14	37	51
3	21 to 30	7	17	24
4	31 to 40	5	9	14
5	41 to 50	2	3	5
6	51 to 60	1	2	3
Total		31	69	100

The most common age group in this study was 11 to 20 years

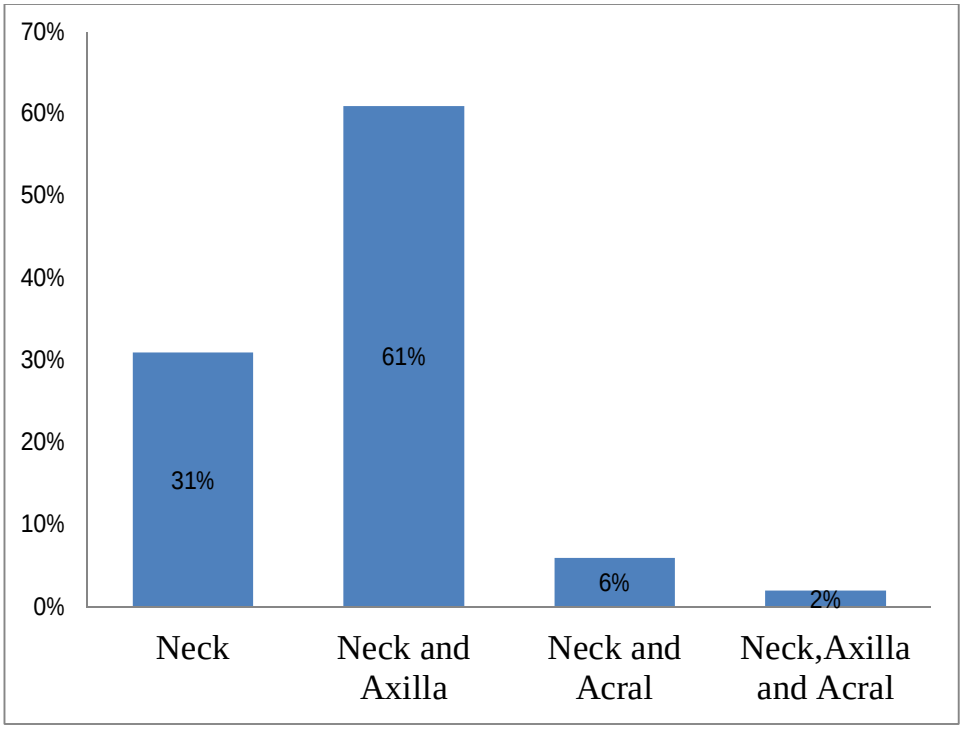
Figure: 1 **SEX DISTRIBUTION**



In our study the number of female patients of Acanthosis Nigricans outnumbers the number of male patients.

Female to male ratio was 2.22: 1.

Figure: 2 **SITE DISTRIBUTION OF ACANTHOSIS NIGRICANS**



Neck was the most common site in this study with 100% of patients showing neck involvement. Next to neck axilla is the second common site involved.

Table : 2 **BODY MASS INDEX (BMI) DISTRIBUTION**

BMI in kg/m^2	**Male**	**Female**	**Total**
< 20	3	4	7
20 - 24.99	9	14	23
25 - 29.99	12	31	43
≥ 30	7	20	27
Total	31	69	100

Body Mass Index is calculated by using the formula weight in kilograms/ height in meter square.

BMI between 25 and 29.99 denotes overweight.

BMI more than or equal to 30 indicates obesity.

In this study 43% of patients were overweight and 27% of patients were obese.

Figure: 3 **BMI DISTRIBUTIONS**

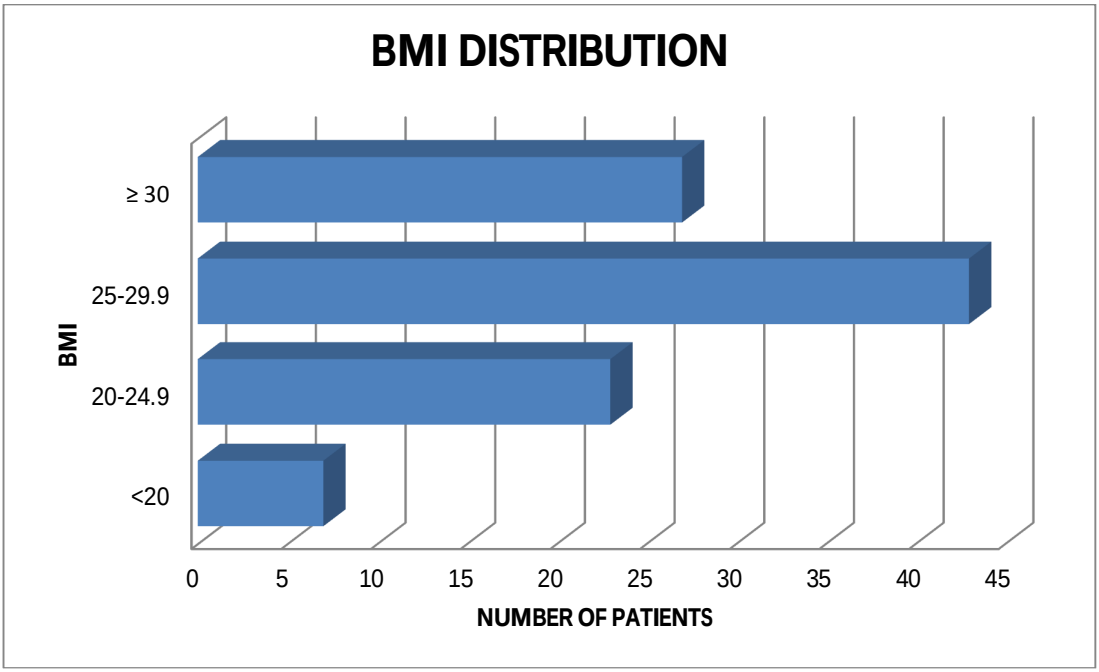
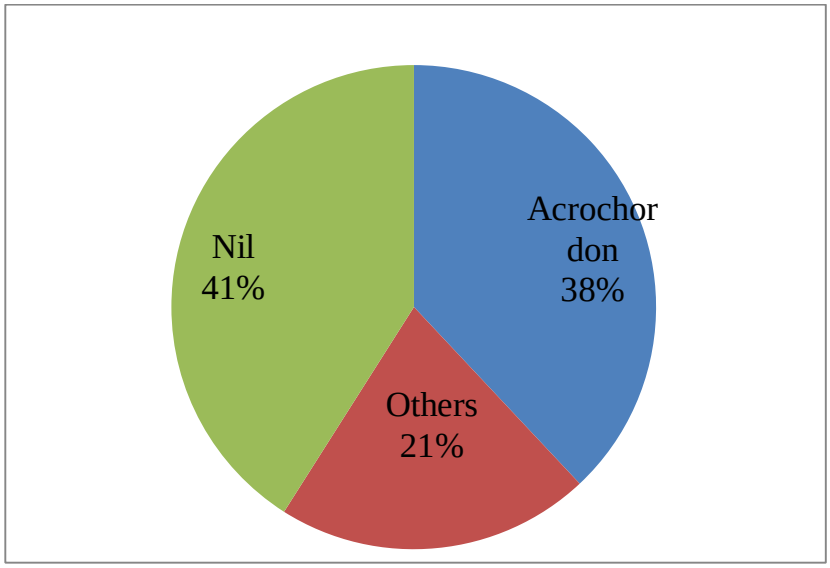


Figure: 4 **ASSOCIATED OTHER DERMATOLOGICAL DISEASES**



All patients with acanthosis nigricans were screened for other dermatological diseases and the following findings were observed.

Acrochordon	–	35
Acne Vulgaris	–	9
Pityriasis versicolor	–	4
Acne vulgaris and Acrochordon	–	3
Seborrheic dermatitis	–	3
Dermatophyte infection	–	2
Polymorphous light eruption	–	2
Psoriasis	–	1
Nil	–	41

In this study acrochordon was the most common associated dermatological finding which was found in 38% of our patients followed by Acne vulgaris which was found in 12% of patients.

In this study 41% of patients had only acanthosis nigricans without any other associated dermatological disease.

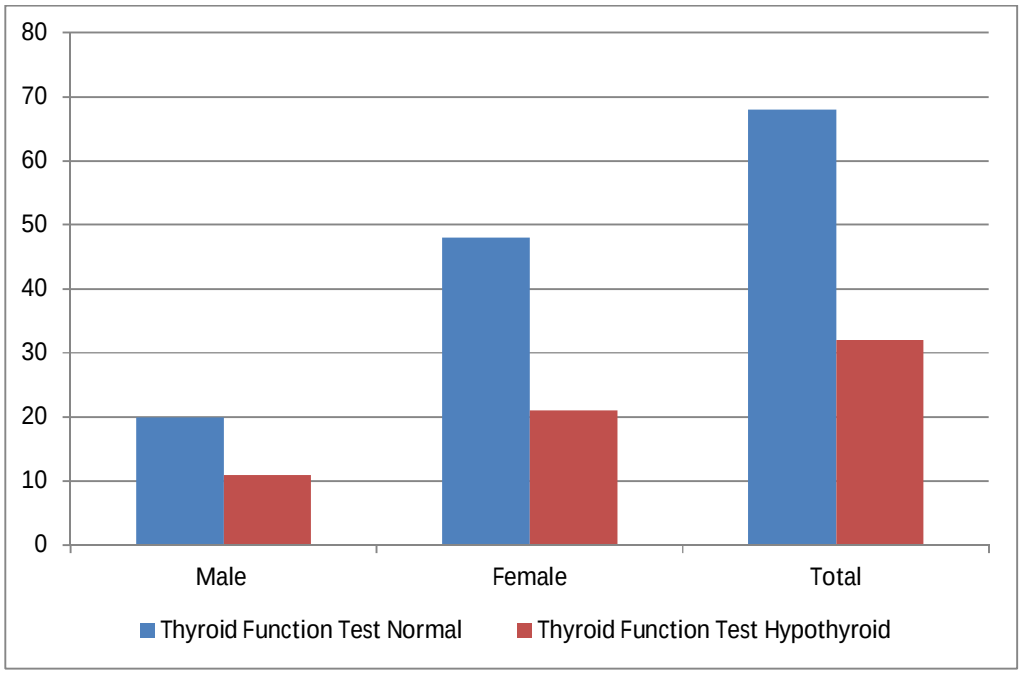
ENDOCRINE TESTS

HYPOTHYROIDISM

Table: 3 **THYROID FUNCTION TEST**

	Normal	**Hypothyroid**	**Percentage**
Male	20	11	35.48
Female	48	21	30.43
Total	68	32	32

Figure: 5 **THYROID FUNCTION TEST**

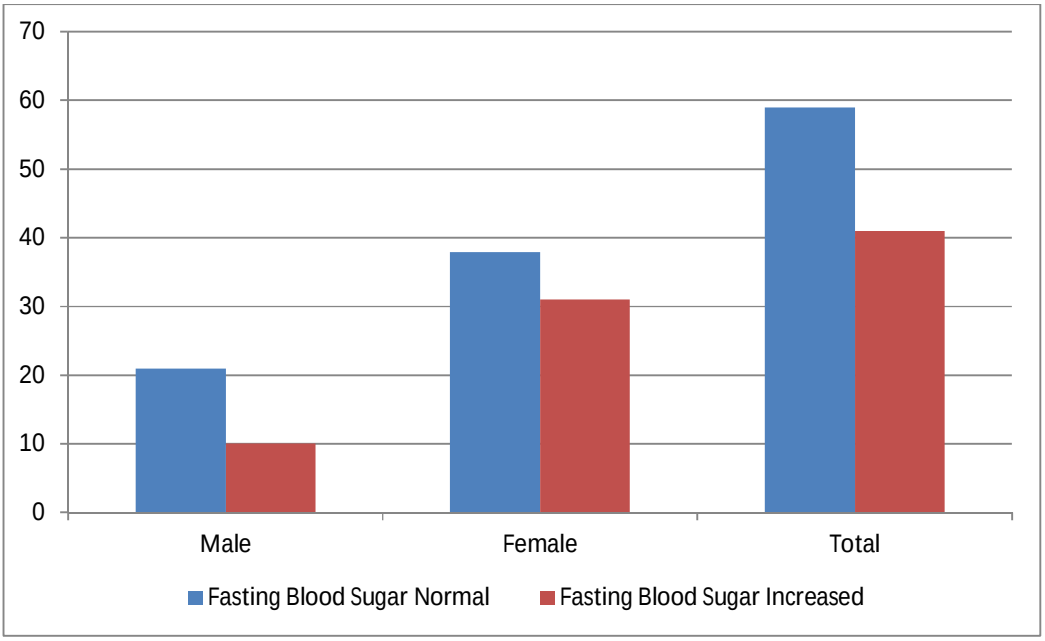


DIABETES MELLITUS

Table: 4 **FASTING BLOOD SUGAR**

	Normal	**Increased**	**Percentage**
Male	21	10	32.25
Female	38	31	44.92
Total	59	41	41

Figure: 6 **FASTING BLOOD SUGAR**



DYSLIPIDEMIA

Table 5: **FASTING LIPID PROFILE**

	Normal	**Abnormal**	**Percentage**
Male	22	9	29.03
Female	44	25	36.23
Total	66	34	34

In this study raised fasting blood sugar was the most common endocrine abnormality present in 41% of patients.

Next to diabetes mellitus abnormal fasting lipid profile was the common finding with 34% of patients having dyslipidemia.

Hypothyroidism was present in 32% of study patients.

FIGURE: 7 **CONSOLIDATED ENDOCRINE FINDINGS**

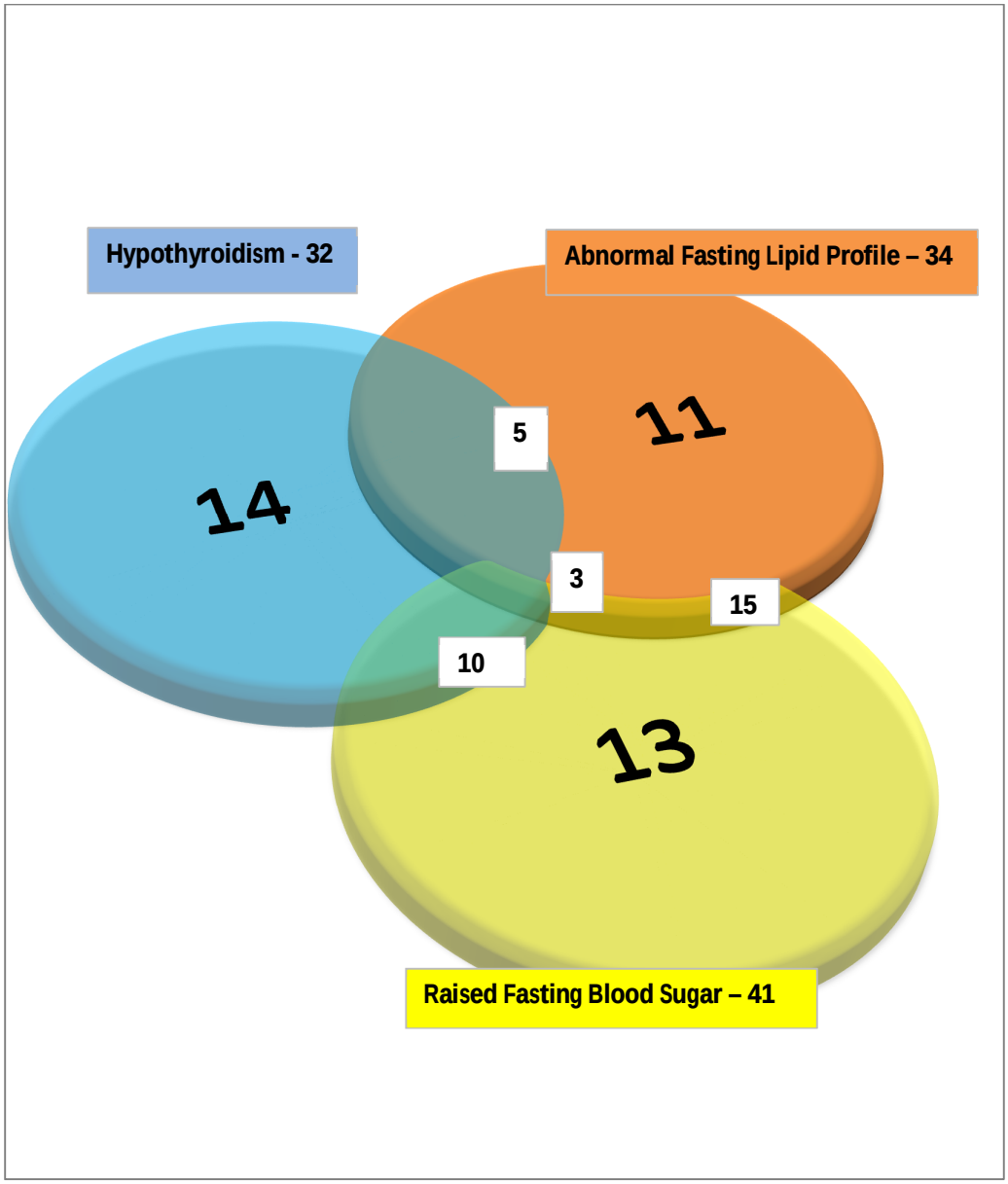
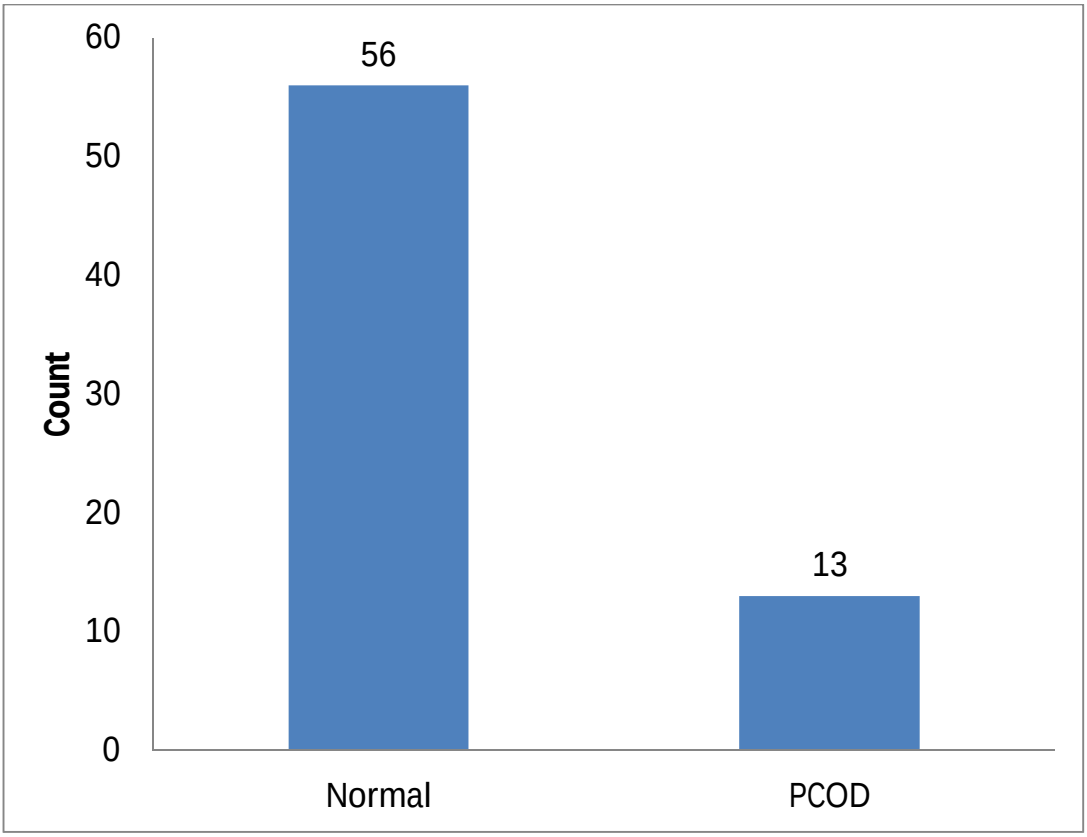


Figure: 8 **ULTRASOUND ABDOMEN**



In this study ultrasound abdomen was done for all female patients. Of the 69 females 13 females were having polycystic ovarian disease. Among the study patients, 18.84% of the females with acanthosis nigricans had associated polycystic ovarian disease.

Figure: 9 **PRE TREATMENT GRADING OF SEVERITY**

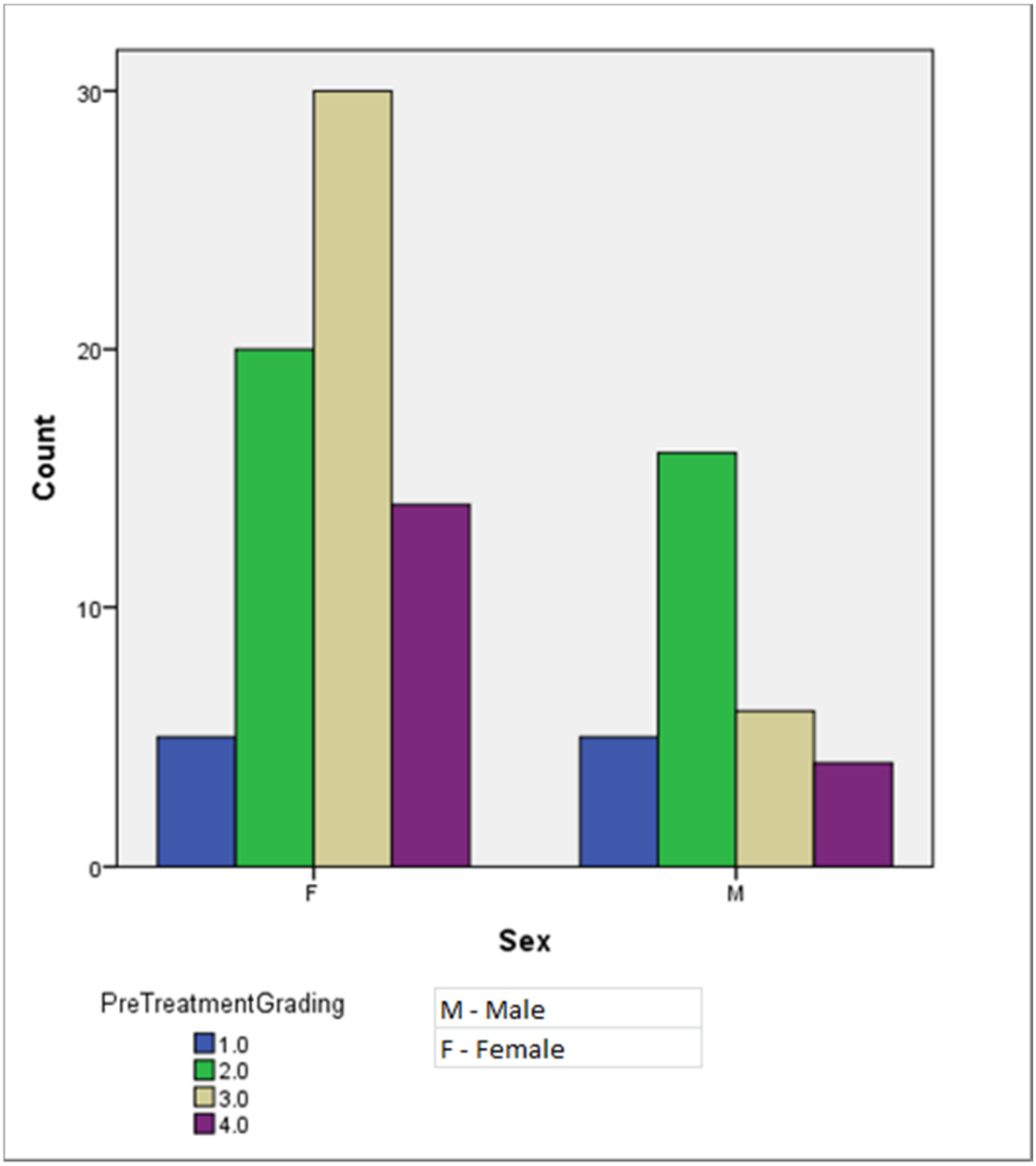


Table: 6 **SEX AND PRE TREATMENT GRADING**

Grade	Male		Female		Total percentage
	Number	% within Sex	Number	% within Sex	
1	5	16.1	5	7.2	10
2	16	51.6	20	29	36
3	6	19.4	30	43.5	36
4	4	12.9	14	20.3	18
Total	31	100	69	100	100

In this study most of the patients presented with grade 2 or grade 3 each of which contributes to 36% of study population.

Eighteen percentage of patients presented with grade 4 severity.

Ten percentage of patients presented with grade 1 severity.

Among the male patients of acanthosis nigricans Grade 2 was the commonest presentation which contributed to 51.16% of male patients.

Among the female patients of acanthosis nigricans Grade 3 was the commonest presentation which contributed to 43.5% of female patients.

Figure: 10 **SEVERITY GRADING DISTRIBUTION**

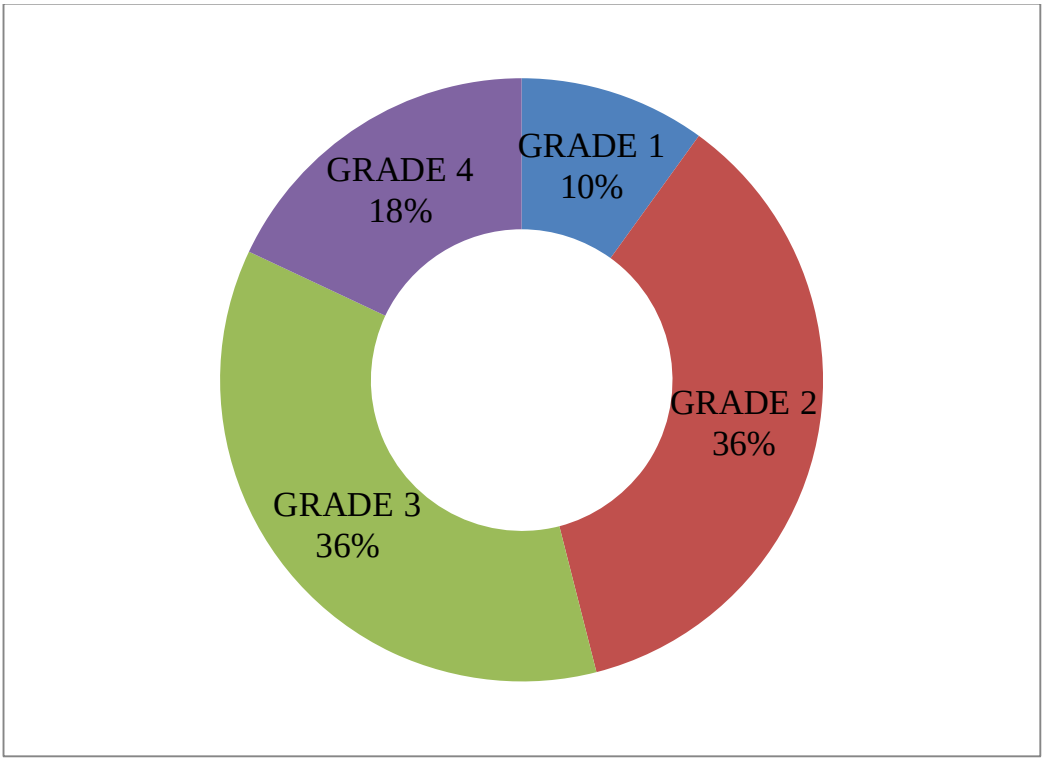
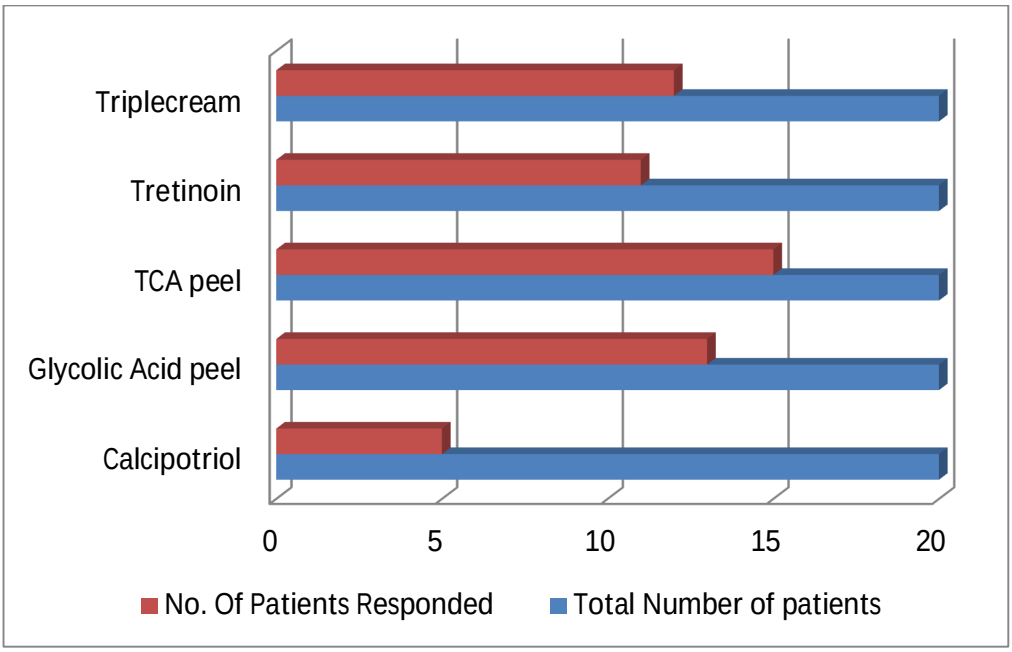


Table: 7 **RESPONSE PERCENTAGE OF DIFFERENT TREATMENTS**

Treatment Given	Total No.	No. Of Patients Responded	% of Response	P value
Calcipotriol	20	5	25	
Glycolic Acid peel	20	13	65	
TCA peel	20	15	75	0.021
Tretinoin	20	11	55	
Triple cream	20	12	60	

Figure: 11 **TREATMENT RESPONSE**



In this study decrease in severity grading from pretreatment grading after treatment was taken as presence of response and if there is no change in severity grading after treatment at the end of study period it was taken as no response.

In this study group of patients treated with Trichloroacetic acid chemical peeling had shown the highest response percentage with 75% of them showing response.

Chemical peeling with glycolic acid has shown the next highest response percentage with 65% of them showing response.

Patients who are treated with topical triple cream showed 60% response and those treated with topical tretinoin showed 55% response.

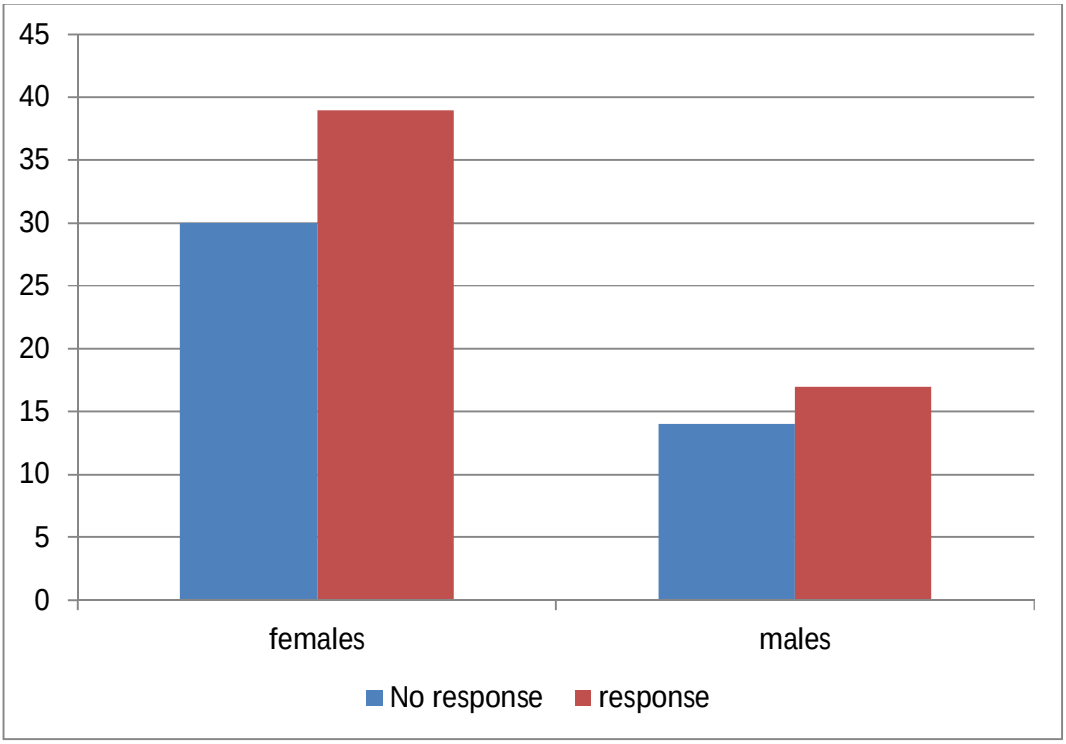
Topical treatment with daily application of calcipotriol has shown the least response percentage with only 25% of them was responding.

Difference in treatment response found among the groups in this study was significant. (p value = 0.021)

Table: 8 **SEX AND RESPONSE**

Sex	Response	No Response	% of Response
Male	17	14	54.83
Female	39	30	56.52
Total	56	44	56

Figure: 12 **SEX AND RESPONSE**

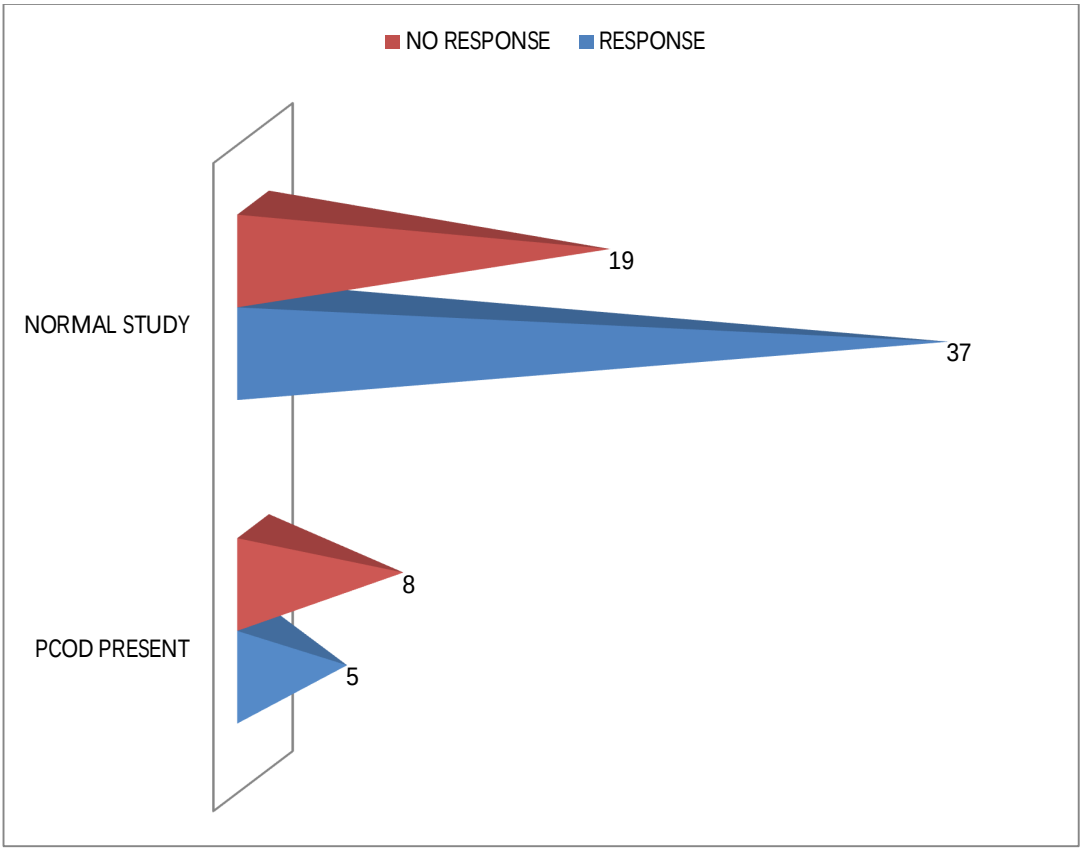


In this study response percentage for both males and females were almost closer with females showing slightly higher response percentage.

Table: 9 **PCOD AND RESPONSE RELATION**

PCOD	Response Present	No Response	% of Response
Present	5	8	38.46
Absent	37	19	66.07

Figure: 13 **ULTRASOUND ABDOMEN AND RESPONSE**



In this study 13 female patients were found to have PCOD on ultrasound abdomen and pelvis screening and the treatment response percentage was 38.46.

In those female patients with normal ultrasound finding the response percentage was 66.07 which was higher than those with PCOD.

Table: 10 **AGE DISTRIBUTION AND RESPONSE**

Age (In Years)	**Response**	**No Response**	**Response Percentage**
< 10	2	1	66.66
11 – 20	29	22	56.86
21 – 30	14	10	58.33
31 – 40	7	7	50
41 – 50	2	3	40
> 50	2	1	66.66

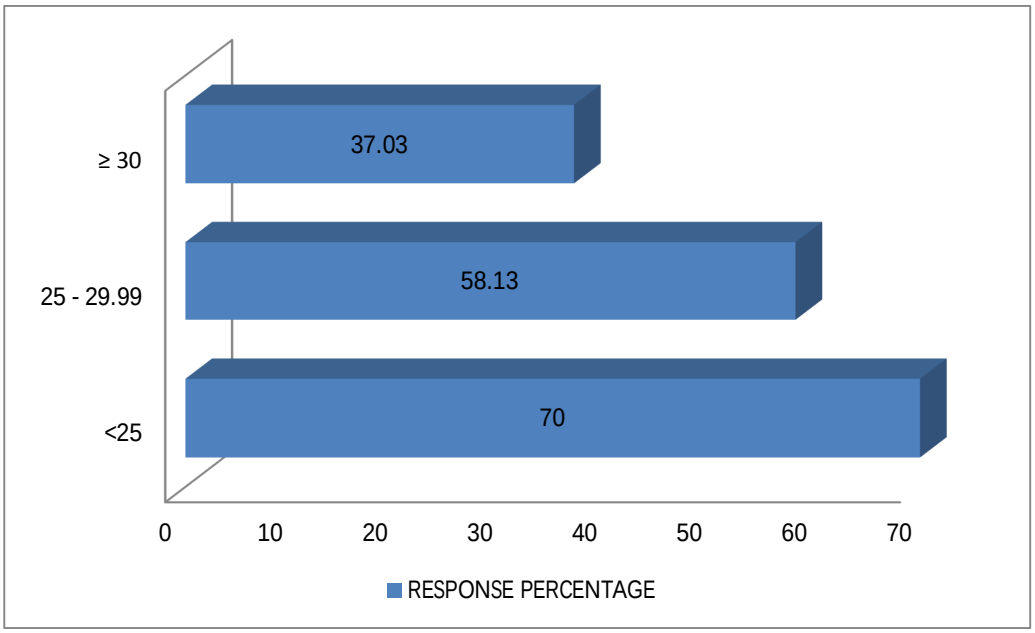
In this study even though patients with extremes of age group showed highest response percentage their count was very low to be taken as significant.

In age groups with adequate number of patients, highest response percentage was found in age group between 21 and 30 years.

Table: 11 **BODY MASS INDEXAND RESPONSE**

BMI	RESPONSE	NO RESPONSE	RESPONSE PERCENTAGE
<25	21	9	70
25 - 29.99	25	18	58.13
≥ 30	10	17	37.03

Figure: 14 **BODY MASS INDEX AND RESPONSE**



In this study the treatment response rate for patients with body mass index less than 25 was 70%.

Those patients who were either overweight or obese with a body mass index more than 25 and less than 30 had a response percentage of 58.13%.

Among patients with body mass index greater than or equal to 30 the response percentage was 37.03%.

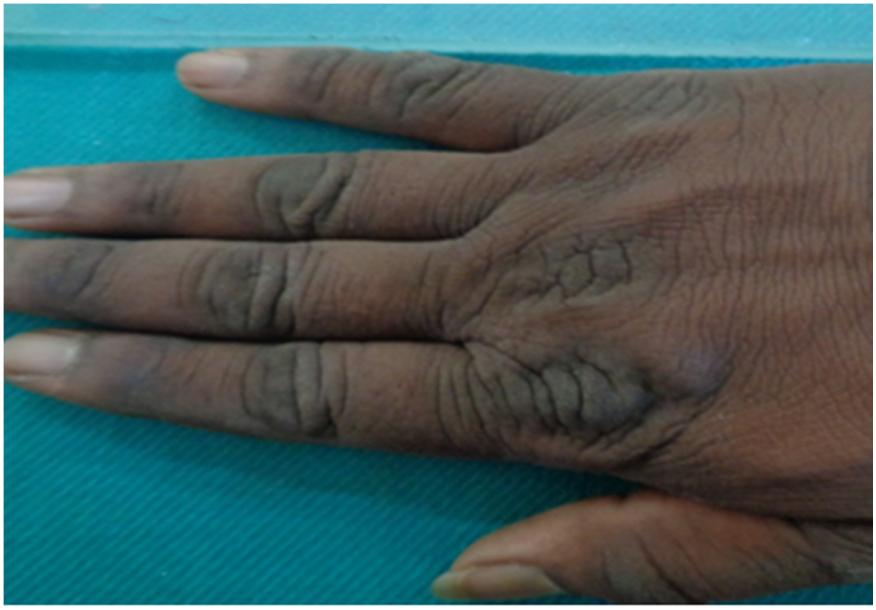


Image 1 and 2: ACRAL ACANTHOSIS NIGRICANS

Image 3: ACANTHOSIS NIGRICANS OF NECK WITH ACROCHORDON

Image 4: ACANTHOSIS NIGRICANS NECK GRADE 1

Image 5: ACANTHOSIS NIGRICANS NECK GRADE 2

Image 6: ACANTHOSIS NIGRICANS NECK GRADE 3

Image 7: ACANTHOSIS NIGRICANS NECK GRADE 4

Image 8 and 9: PRE AND POST TREATMENT WITH TRETINOIN

Image 10 and 11: PRE AND POST TREATMENT

WITH GLYCOLIC ACID

Image 12 and 13: PRE AND POST TREATMENT

WITH TRIPLE CREAM

Image 14 and 15: PRE AND POST TREATMENT

WITH TRICHLOROACETIC ACID

Discussion

DISCUSSION

Acanthosis Nigricans is a common dermatological disease which clinically present as hyperpigmented, hyperkeratotic, verrucous and velvety plaques seen commonly over neck, axilla and extremities.

Acanthosis Nigricans may be a marker of internal diseases like insulin resistance, diabetes mellitus, dyslipidemia, hypothyroidism, polycystic ovarian disease and rarely internal malignancies like gastric carcinoma.

Acanthosis Nigricans may also occur as a side effect of certain drugs and familial cases also been reported.

In this study 100 patients of Acanthosis Nigricans were selected and divided randomly into 5 groups of 20 patients in each group.

Sex Distribution

In this study the number of female patients with Acanthosis Nigricans outnumbered male patients with 69 females and 31 males.

In this study the ratio of female to male patient was 2.22: 1.

This ratio was in concurrence with the previous studies by Neeraj Puri et al [17] which showed a female to male ratio of 3:2 and study by Varthakavi et al [23] which showed a female to male ratio of 3.5:1

Age Distribution

In this study the most common age group was between 11 and 20 years which contributed to about 51% of study population. Also the number of patients in extremes of age group was low with only 3% of patients were aged less than 10 years and another 3% were aged more than 50 years.

This was in concurrence with the previous studies by Neeraj Puri et al [17] where 33.3% of patients were in the age group between 11 to 20 years contributing the highest age group percentage. Also 3.3% of patients were aged less than 10 years and 10 % were more than 50 years of age.

The mean age in our study was 22.24. This was slightly lower than the mean age of previous study by Varthakavi et al [23] where the mean age was 26.3.

Site Distribution of Acanthosis nigricans

In this study neck was the most common site involved with 100% of patients showing neck involvement. Axilla was the second most common site with 63% involvement.

This was in concurrence with the previous study by Varthakavi et al [23] where neck involvement was 100% followed by axilla involvement in 80.6% of patients.

Body Mass Index (BMI)

In this study 43% of patients were overweight and 27% of patients were obese with a BMI more than or equal to 25 kg/meter square. Thus in this study only 30% of patients were having normal BMI.

Associated other Dermatological Diseases

Acrochordon was the most common associated dermatological condition present in 38 % of patients. This was followed by acne vulgaris which occurred in 12% of patients.

This was in concurrence with the study by Neeraj Puri et al [17] where acrochordon was the commonest associated condition present in 26.6% of patients.

Endocrine Dysfunction

In this study Diabetes was the commonest endocrine abnormality with 41% of patients showing raised fasting blood sugar.

Hypothyroidism was present in 32% of study patients and dyslipidemia was present in 34% of patients.

These results were in concurrence with the study by Varthakavi et al [23] where 44.4 % of patients were diabetic with either impaired glucose tolerance test or frankly diabetic profile.

In the study done by Neeraj Puri et al [17] diabetes was present in 30% of patients and hypothyroidism was present in 13.3% of patients which was lower compared to our study.

Poly Cystic Ovarian Disease

In this study on ultrasound screening PCOD was present in 18.84% of female patients with Acanthosis nigricans.

This observation was close to the observation in the study by Neeraj Puri et al [17] where 20% of females were having PCOD.

Pre Treatment Grading

In this study most Acanthosis Nigricans patients presented with either Grade 2 or grade 3 severity.

Among the male patients with acanthosis nigricans Grade 2 was the commonest presentation which contributed to 51.16% of male patients.

Among the female patients with acanthosis nigricans Grade 3 was the commonest presentation which contributed to 43.5% of female patients.

Treatment Response comparison

In this study chemical peeling with trichloroacetic acid had highest response percentage of 75%.

Chemical peeling with glycolic acid had shown the next highest response percentage with 65% of them showing response.

Patients who are treated with topical triple cream showed 60% response and those treated with topical tretinoin showed 55% response.

Patients who were treated with daily application of calcipotriol had the least response percentage of 25%.

Difference found among the treatment groups was statistically significant with a p value of 0.021.

Although some of the patients had shown significant improvement in severity with decrease in Grading from grade 4 to Grade 1, none of the patients showed complete clearance of lesion at the end of the study period. This may be due to shorter duration of treatment. Patients need to be followed up with continuous treatment for a longer period.

Sex and Response

In this study response percentage was almost equal among males and females with 54.83% of males and 56.52% of females showing response to treatment.

PCOD and Response

In this study the response percentage of female patients with PCOD was lower than the female patients without PCOD. Response percentage was 38.46% in female patients with acanthosis nigricans and 66.07% in patients without acanthosis nigricans.

This observation indicates that patients with PCOD were more resistant to treatment and they may need longer period of treatment along with simultaneous treatment for correction of PCOD.

Body Mass Index and Response

In this study the response percentage was higher with those having BMI less than 25 kg/m^2 and the response percentage was lowest with those having BMI more than or equal to 30 kg/m^2.

In this study the treatment response rate for patients with body mass index less than 25 was 70%.

Those patients who were either overweight or obese with a body mass index more than 25 and less than 30 had a response percentage of 58.13%.

Among patients with body mass index greater than or equal to 30 the response percentage was 37.03%

Thus in this study response rate decreases with increasing body mass index.

Conclusion

CONCLUSION

- Acanthosis Nigricans was more common in females as compared to males.
- The most common age group at presentation was 11to 20 years.
- The most common site of involvement of acanthosis nigricans was neck followed by axilla.
- Most patients with acanthosis nigricans in this study had associated obesity with 70% of population falling under either overweight or obese according to body mass index value.
- Acanthosis nigricans was associated with several endocrine diseases with 42% of study population having raised fasting blood sugar, 32% of patients having hypothyroidism and 34% of patients showing dyslipidemia.
- Polycystic ovarian disease was present in 18.84% of female patients with acanthosis nigricans.
- Most patients of acanthosis nigricans presented with either grade 2 or grade 3 severity with males presenting with lower grade than females.

- Treatment response was almost similar among both male and female patients with an average response percentage of 56.
- Patients treated with trichloroacetic acid chemical peeling had the best response percentage while patients treated with topical calcipotriol had the least response percentage.
- Patients treated with glycolic acid chemical peeling, topical tretinoin and topical triple cream had intermediate response percentage.
- None of the treatment modalities used in this study was effective in completely clearing acanthosis nigricans skin lesions. This may be due to shorter treatment period of 12 weeks.
- Patients with polycystic ovarian disease showed less response to treatment compared to those with normal ultrasound finding. It suggests the importance of simultaneous treatment of associated polycystic ovarian disease.
- Response of patients to treatment decreases with increasing body mass index. It suggests the need for weight reduction for better treatment results.

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Annexures

ABBREVIATIONS USED

AN	–	Acanthosis nigricans
IGF-1 R	–	Insulin like growth factor 1 receptor
IGFBP	–	Insulin like growth factor binding proteins
HDL	–	High density lipoprotein
BMI	–	Body mass index
PCOS	–	Polycystic ovarian syndrome
HAIR-AN	–	Hyperandrogenism, Insulin resistance and Acanthosis Nigricans
TGF- α	–	Transforming Growth Factor α
EGF	–	Epidermal Growth Factor
CRABP	–	cytosolic all-*trans* retinoic acid-binding protein
RAR	–	Retinoic acid receptors
RARE	–	Retinoic acid response elements
RXR	–	Retinoid X receptors
TNF-α	–	Tumor necrosis factor α
IFN-γ	–	Interferon γ.
TCS	–	Topical corticosteroid
GCR	–	Glucocorticoid receptor

MASTER CHART

Sl.No	Sex	Age (In Years)	Duration (In YEARS)	Distribution	BMI	Other Cutaneous Lesion	Thyroid Function Test	DM	Fasting Lipid Profile	USG Abdomen	Treatment Given	Pre Treatment Grading	Post Treatment Grading	Response
1	M	23	3	N,AX	26.8	ACRO	N	+	N	-	Tretinoin	2	1	R
2	F	13	3	N,AX	26.1	-	HT	-	N	N	TCA peel	3	1	R
3	F	24	4	N,AX	23.1	-	N	-	AB	N	Triple cream	4	2	R
4	M	15	2	N	31.2	ACNE	HT	-	AB	-	Tretinoin	2	2	NR
5	F	17	5	N,AX	36.3	ACRO	N	-	AB	PCOS	Calcipotriol	3	3	NR
6	F	11	3	N	31.1	-	HT	-	N	N	Triple cream	2	1	R
7	F	37	6	N,AX	27.3	TV	N	-	AB	N	Calcipotriol	2	2	NR
8	M	12	2	N,AX	21.3	-	N	-	N	-	Tretinoin	3	2	R
9	M	11	3	N,AX	22.4	-	HT	-	AB	-	Calcipotriol	2	1	R
10	F	47	6	N,AX	26.3	ACRO	N	+	N	N	Tretinoin	1	1	NR
11	F	15	1	N	32.3	-	N	+	AB	PCOS	TCA peel	4	2	R
12	M	36	5	N,AX	32.2	ACRO	HT	-	N	-	Triple cream	2	2	NR
13	F	14	3	N	25.8	-	N	+	AB	N	Glycolic Acid peel	3	1	R
14	F	13	2	N,AX	18.6	-	HT	-	N	N	Tretinoin	2	1	R
15	F	34	4	N,AX	22.5	ACRO	N	+	N	N	TCA peel	4	2	R
16	M	24	3	N,AX	23.1	TV	N	+	N	-	Triple cream	1	1	NR
17	F	55	5	N,AX	24.3	-	N	-	N	N	Tretinoin	3	2	R
18	F	19	7	N,AX,AC	31.4	ACRO	HT	+	AB	PCOS	TCA peel	3	3	NR
19	F	14	3	N,AX	25.3	ACNE	N	-	N	N	Calcipotriol	2	2	NR
20	M	22	4	N,AC	19.2	ACRO	N	-	N	-	Triple cream	2	1	R
21	F	19	3	N,AX	23.2	SD	N	+	N	N	Tretinoin	2	1	R
22	F	33	2	N,AX	24.5	-	HT	+	N	N	Glycolic Acid peel	3	3	NR
23	M	8	3	N,AX	30.4	-	N	+	AB	-	TCA peel	2	2	NR
24	F	23	4	N,AX	32.5	ACRO	HT	+	N	PCOS	Triple cream	3	3	NR
25	F	12	2	N,AX	26.3	-	N	-	N	N	Glycolic Acid peel	3	2	R

Sl.No	Sex	Age (In Years)	Duration (In YEARS)	Distribution	BMI	Other Cutaneous Lesion	Thyroid Function Test	DM	Fasting Lipid Profile	USG Abdomen	Treatment Given	Pre Treatment Grading	Post Treatment Grading	Response
26	F	15	5	N,AX,AC	27.8	ACNE	N	-	N	N	Calcipotriol	3	3	NR
27	M	42	3	N,AX	25.8	TV	HT	+	N	-	Calcipotriol	2	2	NR
28	F	15	3	N,AX	29.1	TINEA	N	-	N	N	Triple cream	2	1	R
29	F	17	5	N,AC	33.5	ACRO	HT	+	AB	N	Tretinoin	3	3	NR
30	F	11	3	N,AX	26.1	TV	N	-	N	N	TCA peel	2	1	R
31	M	16	3	N,AX	24.3	SD	N	-	N	-	Glycolic Acid peel	4	2	R
32	F	35	3	N	24.1	-	N	+	N	N	Triple cream	1	1	NR
33	F	12	2	N	27.7	-	N	-	N	N	Tretinoin	3	2	R
34	M	37	4	N,AC	27.3	-	HT	-	N	-	TCA peel	2	1	R
35	F	25	3	N,AX	35.3	ACRO	N	+	AB	PCOS	Glycolic Acid peel	2	2	NR
36	M	15	2	N,AX	28.1	ACNE	N	-	AB	-	Triple cream	3	2	R
37	F	18	1	N,AX	19.6	ACRO + ACNE	N	-	N	N	Tretinoin	2	2	NR
38	F	18	5	N,AX	34.1	ACRO	HT	+	N	N	TCA peel	4	2	R
39	M	23	5	N,AX	36.3	ACRO	HT	+	N	-	Glycolic Acid peel	2	1	R
40	F	13	3	N	26.8	-	N	+	N	N	Calcipotriol	2	2	NR
41	F	33	5	N,AX	31.3	ACRO	N	+	N	PCOS	Tretinoin	4	4	NR
42	F	20	3	N,AX	36.4	PLE	N	-	AB	N	Triple cream	4	2	R
43	M	13	1	N	28	-	HT	-	AB	-	TCA peel	3	1	R
44	F	19	3	N,AX	31.3	ACRO	N	-	AB	N	Glycolic Acid peel	2	2	NR
45	M	33	4	N,AX	19.6	PSORIASIS	HT	-	N	-	Glycolic Acid peel	2	1	R
46	F	37	6	N,AX	21.4	-	N	-	N	N	Calcipotriol	4	3	R
47	M	19	4	N	31.3	ACRO	HT	+	N	-	Triple cream	2	2	NR
48	F	13	1	N,AX	32.3	ACNE	N	-	AB	N	Tretinoin	2	2	NR
49	F	12	3	N,AX	19.2	-	N	-	N	N	TCA peel	3	1	R
50	F	31	3	N,AX	28.3	ACRO	N	+	AB	PCOS	Triple cream	3	2	R
51	M	14	2	N,AX	28.6	-	N	+	N	-	Tretinoin	3	2	R

Sl.No	Sex	Age (In Years)	Duration (In YEARS)	Distribution	BMI	Other Cutaneous Lesion	Thyroid Function Test	DM	Fasting Lipid Profile	USG Abdomen	Treatment Given	Pre Treatment Grading	Post Treatment Grading	Response
52	M	35	2	N,AX	22.6	-	N	-	N	-	Calcipotriol	2	2	NR
53	F	32	2	N,AC	23.1	-	N	+	N	N	Glycolic Acid peel	3	1	R
54	F	17	3	N,AX	33.4	ACRO	HT	-	AB	N	Glycolic Acid peel	4	2	R
55	F	11	1	N	22.3	-	N	-	N	N	TCA peel	4	1	R
56	M	7	2	N,AX	21.7	-	N	-	N	-	Glycolic Acid peel	3	1	R
57	F	24	3	N,AX	28.9	-	HT	+	N	N	Tretinoin	3	2	R
58	F	43	4	N,AX	26.1	ACRO	N	-	AB	N	Triple cream	2	1	R
59	F	27	5	N	31.7	ACRO	N	+	AB	N	Calcipotriol	3	2	R
60	M	13	1	N	30.4	-	N	+	AB	-	TCA peel	2	1	R
61	F	18	5	N	27.3	ACRO	HT	+	N	N	Glycolic Acid peel	1	1	NR
62	F	13	5	N,AX	24.1	ACNE	N	-	N	N	Glycolic Acid peel	3	2	R
63	F	25	5	N,AX	25.2	ACRO	N	+	N	PCOS	Tretinoin	2	2	NR
64	M	43	5	N,AC	35.6	ACRO	HT	-	N	-	Triple cream	1	1	NR
65	F	29	5	N,AX	23.5	-	N	-	N	N	Calcipotriol	1	1	NR
66	F	12	3	N	25.7	-	N	+	N	N	TCA peel	2	2	NR
67	F	15	3	N,AX	35.4	-	N	-	AB	N	Calcipotriol	3	3	NR
68	M	12	3	N	22.5	-	HT	+	N	-	Tretinoin	1	1	NR
69	F	25	2	N,AC	26.3	ACRO + ACNE	N	-	AB	N	Triple cream	2	1	R
70	F	20	2	N,AX	26.9	ACRO	HT	-	N	N	Glycolic Acid peel	4	2	R
71	M	23	2	N,AX	18.2	ACRO	N	-	N	-	TCA peel	4	1	R
72	F	39	4	N	18.3	-	N	-	N	N	Glycolic Acid peel	2	1	R
73	F	23	3	N,AX	30.6	ACRO	N	+	AB	PCOS	Calcipotriol	3	3	NR
74	F	19	3	N	22.5	ACNE	N	-	N	N	Triple cream	2	1	R
75	F	27	4	N	25.4	ACRO	N	+	N	PCOS	TCA peel	3	2	R
76	M	54	8	N	29.4	ACRO	HT	-	AB	-	Calcipotriol	1	1	NR
77	M	24	4	N,AX	24.8	PLE	N	-	AB	-	Glycolic Acid peel	3	2	R

Sl.No	Sex	Age (In Years)	Duration (In YEARS)	Distribution	BMI	Other Cutaneous Lesion	Thyroid Function Test	DM	Fasting Lipid Profile	USG Abdomen	Treatment Given	Pre Treatment Grading	Post Treatment Grading	Response
78	F	51	10	N	25.3	ACRO	N	-	N	N	TCA peel	3	1	R
79	F	22	3	N	36.3	ACRO	HT	+	N	N	Calcipotriol	3	2	R
80	F	21	2	N,AX	27.4	SD	N	-	N	N	Glycolic Acid peel	1	1	NR
81	F	20	3	N,AX	34.3	ACRO	HT	-	N	N	Triple cream	2	2	NR
82	F	24	4	N	26.3	-	N	+	AB	PCOS	Tretinoin	3	2	R
83	M	33	3	N	22.6	ACRO	N	-	N	-	TCA peel	1	1	NR
84	F	17	3	N,AX	31.8	ACRO	N	+	AB	PCOS	Glycolic Acid peel	3	3	NR
85	F	18	2	N	26.2	-	HT	+	AB	N	Calcipotriol	2	2	NR
86	F	48	6	N	25.9	ACRO	N	-	N	N	Triple cream	4	3	R
87	M	17	3	N	28.1	-	HT	-	N	-	Tretinoin	2	2	NR
88	M	13	2	N	25.4	ACNE	N	-	N	-	Calcipotriol	2	1	R
89	F	23	3	N,AX	21.3	TINEA	HT	-	N	N	TCA peel	3	3	NR
90	F	9	2	N,AX	20.9	-	N	-	N	N	Tretinoin	3	2	R
91	F	13	3	N,AX	28.6	-	HT	-	N	N	Calcipotriol	4	4	NR
92	M	12	3	N,AX	26.3	-	N	+	AB	-	Glycolic Acid peel	4	2	R
93	M	27	4	N,AX	26.9	ACRO + ACNE	N	-	N	-	Triple cream	2	2	NR
94	F	14	2	N	29.3	-	N	+	AB	N	TCA peel	3	1	R
95	F	23	3	N	26.5	ACNE	HT	-	N	N	Glycolic Acid peel	4	4	NR
96	F	15	3	N,AX	27.1	-	N	+	AB	N	Calcipotriol	3	3	NR
97	F	13	2	N	36.1	-	N	+	AB	N	Tretinoin	4	3	R
98	F	25	3	N,AX	26.9	ACRO	N	-	N	N	Triple cream	3	2	R
99	M	11	1	N	27.3	-	HT	-	N	-	Calcipotriol	4	4	NR
100	F	18	2	N,AX	28.3	ACRO	N	+	AB	PCOS	TCA peel	3	2	R

KEY FOR MASTER CHART

SEX

M - MALE
F - FEMALE

DISTRIBUTION

N - NECK
AX - AXILLA
AC - ACRAL

BMI – BODY MASS INDEX IN WEIGHT IN KILOGRAMS / HEIGHT IN METER SQUARE

OTHER CUTANEOUS LESION

ACRO - ACROCHORDON
PLE - POLYMORPHOUS LIGHT ERUPTION
SD - SEBORRHEIC DERMATITIS
TV - TINEA VERSICOLOR
TINEA - TINEA CORPORIS
PSORA - PSORIASIS VULGARIS

THYROID FUNCTION TEST

HT - HYPOTHYROID
N - NORMAL

DM - DIABETES MELLITUS

FASTING LIPID PROFILE

AB - ABNORMAL
N - NORMAL

USG ABDOMEN

PCOS - POLY CYSTIC OVARIAN SYNDROME
N - NORMAL

TREATMENT GIVEN

TCA PEEL – TRICHLOROACETIC ACID PEEL

RESPONSE

R - RESPONDED
NR - NO RESPONSE

PROFORMA

Case No:

PATIENT DETAILS:

Name: Age: Sex: OP No:

Address: Occupation:

Main Complaints:

H/O present illness;
- Duration of illness
- Sites involved
- Progression

H/O of increased frequency of micturition, increased appetite
H/O gain or loss of weight
H/O altered bowel habits, intolerance to heat and cold
H/O abdominal pain, melena
H/O breathlessness, chest pain, chronic cough
H/O drug intake for any chronic illness

Family History:

Marital/menstrual History:

Associated dermatological disorders:
- Acne
- Skin tag.
- Seborrhoeic dermatitis
- other dermatological conditions

CLINICAL EXAMINATION:

General examination :
- Height
- Weight
- Body Mass Index

Generalised lymphadenopathhy

Pulse:	BP:
RR:	Temp:
Pallor:	Icterus:
CVS:	RS:

P/A:
CNS

Bones and joints

DERMATOLOGICAL EXAMINATION:

Site of involvement: Nape of neck/ axilla/ groin/ extremities

Pretreatment severity Grading:

Palms and soles:
Oral and genital Mucosa:
Hair and nail:

Investigations

1. Blood haemogram
2. Blood sugar fasting and postprandial
3. RFT
4. LFT
5. Blood lipid profile
6. Fasting serum insulin level.
7. Thyroid function test
8. USG abdomen

TREATMENT:
Group:
Regimen given:

FOLLOW UP:
Complaints

Grading

Side effects

INFORMATION SHEET

TITLE : **"ACANTHOSIS NIGRICANS – A CLINICOEPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY"**

Name of Investigator: Dr.E.Balasubramanian

Name of Participant:

Purpose of Research: The purpose of this study is to determine the clinical profile, common associated endocrinological disorder and comparing treatment options in patients with Acanthosis nigricans.

Study Procedures: In this study history of patient will be taken, examination and routine blood test will be taken, endocrinological evaluation will be done. The patients are then randomly grouped into 5 groups of 20 numbers each

Group A - Topical 0.05% tretinoin daily application
Group B - Topical 0.005% calcipotriol daily application.
Group C - Topical triple combination cream containing Hydroquinone 2%, Tretinoin 0.05% and Fluocinolone Acetonide 0.01% daily application
Group D - Chemical peeling with 35% Trichloroacetic acid once in every 3 weeks
Group E - Chemical peeling with 50% Glycolic acid once in every 3 weekss
.

Possible Risks : No risks to the patient

Possible benefits

To patient: Any underlying endocrinological problems will be detected and the patient is provided with any of the above mentioned treatments for his primary complaint.

To doctor & to other people: The results of the study will help in identifying the commonest endocrinological diseases associated with acanthosis nigricans patients and also to determine the most effective treatment for acanthosis nigricans. This will help in providing better and complete treatment to other patients in future.

Confidentiality of the information obtained from you: The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Can you decide to stop participating in the study: Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time

How will your decision to not participate in the study affect you: Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant

Date :
Place :

PATIENT CONSENT FORM

Title of the study:

ACANTHOSIS NIGRICANS – A CLINICOEPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY

Name of the Principal investigator: Dr.E.Balasubramanian.

Name of the Institution: Rajiv Gandhi Government General Hospital, Chennai

Patient's Name :
Patient's Age :
Out Patient No :

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment ❑

Signature/thumb impression
Signature/thumb impression

Signature of Investigator
Study Investigator's Name:

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சியாளர்கள் : **டாக்டர். இ. பாலசுப்பிரமணியன்**
டாக்டர். க. மனோகரன்
டாக்டர். க. உமாமகேஸ்வரி

பங்கேற்பாளரின் பெயர் :

தலைப்பு : தோல்தடிமன் மற்றும் கருமை நோயின் (Acanthosis Nigricans) காரணிகளை கண்டறிதல் மற்றும் அதற்கான சில சிகிச்சை முறைகளின் பலன்களை ஒப்பிடுதல் ஆய்வு.

- தங்களை இந்த ஆராய்ச்சியில் பங்கேற்குமாறு கேட்டுக் கொள்கிறேன். இந்த படிவத்தில் உள்ள தகவல் மூலமாக இந்த ஆராய்ச்சியில் பங்கு கொள்ளலாமா என்பதை தீர்மானித்து கொள்ளவும். தங்களுக்கு ஏதேனும் சந்தேகம் இருந்தால் எவ்வித தயக்கமும் இன்றி கேட்டுக் கொள்ளலாம்.
- தோல் தடிமன் மற்றும் கருமை அடைதல் நோயின் காரணிகளை கண்டறிவதும், அதனுடன் தொடர்புடைய நாளமில்லா சுரபிகளின் பிரச்சனைகளை கண்டறிவதும், அந்த நோய்க்கான சில சிகிச்சை முறைகளின் பலன்களை ஒப்பீடு செய்வதும் இந்த ஆராய்ச்சியின் நோக்கம்.
- இந்த ஆய்விற்காக இரத்த பரிசோதனைகள் மற்றும் வேறு மருத்துவ பரிசோதனைகள் செய்வதற்கான அவசியம் எடுத்துரைக்கப்பட்டது.
- ஆராய்ச்சியில் நோயாளியின் அடையாளம் பாதுகாக்கப்படும். ஆராய்ச்சித் தகவல்கள் பகிர்ந்து கொள்ளப்படும் போது தனிப்பட்ட முறையில் அடையாளம் காணக்கூடிய எந்த தகவலும் பகிர்ந்து கொள்ளப்படமாட்டாது.
- இந்த ஆய்வின் இறுதியில் ஆய்வின் முடிவுகள் உங்களிடம் தெரிவிக்கப்படும்.

ஆராய்ச்சியாளரின் கையொப்பம் பங்கேற்பவரின் கையொப்பம்

தேதி :

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு : தோல்தடிமன் மற்றும் கருமை நோயின் (Acanthosis Nigricans) காரணிகளை கண்டறிதல் மற்றும் அதற்கான சில சிகிச்சை முறைகளின் பலன்களை ஒப்பிடுதல் ஆய்வு.

பெயர் : தேதி :

வயது : நோயாளி எண் :

பால் : ஆராய்ச்சி சேர்க்கை எண் :

- இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்குத் தெளிவாக விளக்கப்பட்டது.
- எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.
- எனக்கு இந்த ஆராய்ச்சி பற்றின விவரங்கள் தெளிவாக எடுத்துரைக்கப்பட்டது.
- என்னுடைய உரிமைகளையும் பொறுப்புகளையும் ஆராய்ச்சியாளர் தெளிவுபடுத்தினார்.
- நான் கடந்த ஒரு வருடமாக அல்லது தற்பொழுது எடுத்து கொள்கிற சிகிச்சை பற்றியும் மற்றும் இயற்கை மருத்துவம் பற்றியும் எடுத்துரைத்தேன்.
- ஆராய்ச்சியாளருடன் முழுமையாக ஒத்துழைக்க உறுதியளிக்கிறேன். எந்தவித அசாதாரணமான நிகழ்வுகளையும் உடனடியாக தெரியப்படுத்த உறுதியளிக்கிறேன்.
- நான் இதுவரைக்கும் எந்த ஆராய்சசியிலும் பங்கேற்றதில்லை என்பதை தெரிவித்து கொள்கிறேன்.
- இந்த ஆராய்ச்சியில் எனது சொந்த விருப்பத்தின் பேரில் பிறரின் நிர்பந்தமின்றி நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியில் இருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.
- என்னிடமிருந்து பெறப்பட்ட தகவல்களை அரசாங்கத்திடமோ, நிறுவன நெறிமுறைகள் குழுவிடமோ தெரிவிக்க நான் அனுமதியளிக்கிறேன்.

- ஆராய்ச்சியில் நோயாளிகளின் அடையாளம் பாதுகாக்கப்படும் எவரிடமும் பகிர்ந்து கொள்ளப்படமாட்டாது.

- நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் என்னை இந்த மருத்துவ ஆராய்ச்சியில் சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

- இந்த ஆராய்ச்சியில் தொடர்ந்து நீடிக்க முடிவு எடுத்துள்ளேன்.

- இந்த ஆராய்ச்சியில் ஏதேவது சந்தேகம் இருந்தால், கீழே குறிப்பிட்டுள்ள ஆராய்ச்சியாளரை தொடர்பு கொள்ளுமாறு எடுத்துரைக்கப்பட்டது.

- இந்த ஒப்புதல் படிவத்தில் கையெழுத்திடுவது மூலம் இந்த படிவத்தில் உள்ள தகவல்கள் அனைத்தும் எனக்குப் புரியும்படி விளக்கிக் கூறப்பட்டது என்பதும் இதன் நகல் எனக்கு வழங்கப்பட்டது என்றும் உறுதி கூறுகிறேன்.

பங்கேற்பாளரின் பெயர், கையொப்பம் / இடதுகை பெருவிரல் ரேகை

.....	.....	.....
பெயர்	கையெழுத்து / விரல்ரேகை	தேதி

பாரபட்சமற்ற சாட்சியின் பெயர், கையெழுத்து / இடதுகை பெருவிரல் ரேகை

.....	.....	.....
பெயர்	கையெழுத்து / விரல்ரேகை	தேதி

ஆராய்ச்சியாளர் பெயர் மற்றும் கையெழுத்து

.....	.....	.....
பெயர்	கையெழுத்து	தேதி

***

பங்கேற்பாளரின் பெற்றோர் அல்லது காப்பாளரின்
பெயர், கையொப்பம் / இடதுகை பெருவிரல் ரேகை

.....	.....	.....
பெயர்	கையெழுத்து	தேதி

பாரபட்சமற்ற சாட்சியின் பெயர், கையெழுத்து / இடதுகை பெருவிரல் ரேகை

.....	.....	.....
பெயர்	கையெழுத்து / விரல்ரேகை	தேதி

ஆராய்ச்சியாளர் பெயர் மற்றும் கையெழுத்து

.....	.....	.....
பெயர்	கையெழுத்து	தேதி

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. E.Balasubramanian
Postgraduate M.D.(DVL),
Madras Medical College,
Chennai – 600 003.

Dear Dr. E.Balasubramanian,

The Institutional Ethics Committee has considered your request and approved your study titled **"ACANTHOSIS NIGRICANS A CLINICO EPIDEMIOLOGICAL AND THERAPEUTIC COMPARISON STUDY ".**

No.14112014.

The following members of Ethics Committee were present in the meeting held on 11.11.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director i/c, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10.Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

VICE PRINCIPAL
MADRAS MEDICAL COLLEGE
CHENNAI-3.